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REGULATION OF BLOOD PRESSURE LEVELS BY HEXAMETHONIUM BROMIDE AND MECHANICAL DEVICES

BY

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Received June 16, 1951

Probably the first studies of the pharmacology of quaternary ammonium compounds were made by Crum-Brown and Fraser in 1868. Burn and Dale (1915) found that, unlike nicotine, tetra-ethyl-ammonium chloride blocked autonomic ganglia without noticeable initial stimulation. Barlow and Ing (1948*a* and *b*), Paton and Zaimis (1948*a* and *b*), and Balaban *et al.* (1949) studied the properties of some chemical relatives of tetra-ethyl-ammonium in which two quaternary nitrogen groups were separated by a chain of CH_2 groups. It was found that decamethonium with ten CH_2 groups was curare-form, and pentamethonium and hexamethonium with respectively five and six CH_2 groups were predominantly ganglion blocking agents. For example, Paton and Zaimis (1949) showed that intravenous injection of pentamethonium iodide relaxed the cat's nictitating membrane which had been caused to contract by preganglionic stimulation. Pentamethonium iodide also prevented the pulse-slowing action of vagal stimulation. Kay and Smith (1950) showed that hexamethonium iodide lessened the secretory response to insulin-induced hypoglycæmia but did not prevent the response of gastric secretion to histamine. All of these results are consistent with the view that penta- and hexamethonium salts act chiefly by blocking autonomic ganglia.

Organe *et al.* (1949), and Arnold and Rosenheim (1949) showed that intravenous or intramuscular injections of pentamethonium produced falls of blood pressure in subjects with normal or raised blood pressure. The effect was similar to that of tetra-ethyl-ammonium chloride but lasted longer and was accompanied by fewer subjective sensations. These authors also noted postural hypotension, and Arnold and Rosenheim concluded that postural hypotension was likely to limit the value of the substance in treatment and that the most promising application was to peripheral vascular disease. Arnold *et al.* (1949) showed an increase in the flow through the fingers using a finger plethysmograph. Burt and Graham (1950) confirmed the existence of peripheral dilatation in the legs by skin temperature methods but they found little change in the circulation through the arms.

Restall and Smirk (1950) made therapeutic use of the postural hypotension to enhance the blood pressure lowering effect of penta- and hexamethonium in patients with high blood pressure. They reported encouraging results which further observations have confirmed (Smirk, 1950*a* and *b*; Smirk and Alstad, 1951). They report that a salt-free diet may enhance the effect of methonium salts, an effect of practical importance. Additional clinical reports have been published by Turner (1950), Saville (1950) and Campbell and Robertson (1950) with varying degrees of benefit.

The present paper is concerned with the circulatory effect of hexamethonium bromide (*H.M.B.*) in man. Many similar experiments have been made with pentamethonium bromide (*P.M.B.*) and no substantial difference in their effects has been detected.

METHODS

Plethysmographs used were modifications of those described by Drury and Jones (1927). Water at 33° C. was employed as the medium for transmitting volume changes. In the case of the upper limb, the forearm was horizontal and about 20 cm. below the angle of Louis.

Venous pressures were measured in an antecubital vein by the method of Cohen (1936), the angle of Louis being taken arbitrarily as a zero point.

Ballistocardiograms were used to register induced changes in the cardiac output in the sitting posture. The apparatus will be described elsewhere.

The application of negative or positive pressure to the lower two-thirds of the body requires a suitable pump and a rigid air-tight container in which the patient stands or lies. The junction of the patient's chest to this container is achieved with sheet-plastic applied in such a way that the seal with the skin is actually made by the air pressure—negative or positive as the case may be (Fig. 1). It is essential to support this junction sheet, on the inside for negative pressures and on the outside for positive ones, as even with moderate pressures the total force exerted over its whole area is not inconsiderable. The equipment used to achieve this was made and assembled in the following way.

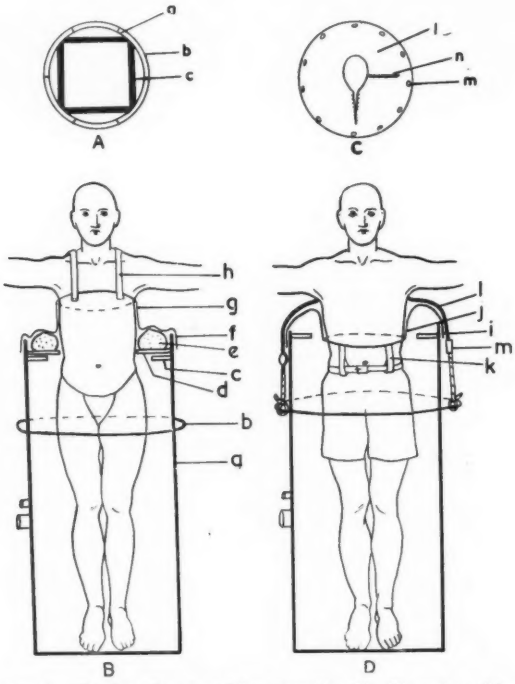

FIG. 1.—Devices for exercising negative (A, B) and positive (C, D) air pressures upon the external surface of the lower two-thirds of the body.

Two tubes are let into the metal drum (a). The smaller is connected to a manometer and the larger ($\frac{3}{4}$ inch) by wide-bore hose to a large capacity pump (Burdick, U.S.A.) variable for compression or suction at will.

For the application of a negative pressure (Fig. 1A and B) the subject, with the chest bare, stands in the metal drum (a). The axillae should clear the top by a few inches. A pair of plywood half circles (d) are now slipped into place resting inside the drum on the metal strips (c). They are cut so as to fill the gap between the metal drum and the patient's chest. A " sausage " (e) made of cloth filled with chaff is now placed on the plywood encircling the subject and is moulded so as to further fill the gap between the drum edge and the chest wall. Next the plastic tube (f, g) is pulled

down over the patient's head, the lower end (f) being sealed to the drum with sticking plaster or an elastic bandage. The upper end (g) will be but loosely applied to the chest and held up by the shoulder straps (h). This plastic tube with its shoulder straps is like a singlet but much wider at the bottom. If suction is now commenced (negative pressure should be used only with great caution if the patient is still erect) sealing occurs automatically if the plastic is momentarily held against the chest wall. The strain is taken by the shoulder straps and " sausage " on the plywood. There must be no large gaps between the patient and the drum or the plastic will balloon through and burst. With this method negative pressure of from 2–100 mm. Hg are readily obtained. A good sealing usually occurs even at low pressures but rarely a smear of vaseline is necessary.

For the application of a positive pressure (Fig. 1C and D) a plastic tube (i, j) similar to that used for negative pressure experiments makes the seal between the patient's skin and the top of the drum. It is lightly held to the skin by a rubber bandage (not shown) and firmly bound to the outside of the drum. The plastic tube is prevented from ballooning under a positive pressure first by calico strips (k) holding down the free edge to a belt worn for the purpose, and secondly by a strong calico sheet (l) with a central hole to admit the patient's thorax. The size of the hole is adjusted by zip fasteners (n) so as to bring the sheet in close apposition to the chest wall. The perimeter of the sheet (l) is tied firmly by cords through the eyelet holes (m) to the iron hoop (b) on the drum. Pressures of 100 mm. Hg are obtainable.

Further practical details are obtainable from the authors.

RESULTS

Effect of Hexamethonium Bromide on Limb Volume

Patients were at rest in the sitting posture with a forearm and a leg, to upper calf level, each in a plethysmograph. The forearm was horizontal and held some 20–30 cm. below the angle of Louis throughout the experiment. When the leg and the arm volumes were approximately steady *H.M.B.* was injected in doses of 20 mg. intravenously or 20–50 mg. subcutaneously. *Following injection, the leg volume increased. The arm volume sometimes increased and sometimes decreased* (Fig. 2). The increase in leg volume in 8 observations varied but lay between 15 and 80 ml. per 2000 ml. of limb immersed in the water of the plethysmograph. The changes in arm volume in 8 observations ranged from an increase of 20 ml. to a decrease of 14 ml. Variation in the direction of change in forearm volume is not surprising. The comparatively small volume increase in the legs might be explained by the fact that an external counter-pressure is imposed on the leg by the water in the leg plethysmograph.

Effect of H.M.B. on the Venous Pressure in High Blood Pressure, Congestive Heart Failure, and Superior Vena Cava Obstruction

In hypertensives without heart failure following intravenous or, in a few instances, subcutaneous administration of *H.M.B.* there was a fall of 1–4 cm. of water pressure and in some instances it was noted that the venous pressure began to fall before the arterial pressure had decreased. Observations were made also in patients with congestive heart failure whose venous pressures could be measured readily by inspection of the external jugular veins (Lewis, 1943). *The venous pressure fell distinctly in all these patients and in* 4 *of them there was at the same time a decrease in breathlessness.*

Effect of an Externally Applied Counter-Pressure upon Postural Hypotension induced by H.M.B.

If the increase in leg volume and the decrease in venous pressure induced by *H.M.B.* are to be explained in part by inability of vessel walls to resist the hydrostatic pressure of blood within them, any fall of blood pressure so induced should not be so great if rubber bandages are applied to the legs and abdomen. *We found, however, that pressure on the abdomen or elastic binding of the legs including the thighs, or both procedures combined were not fully effective methods of restraining the*

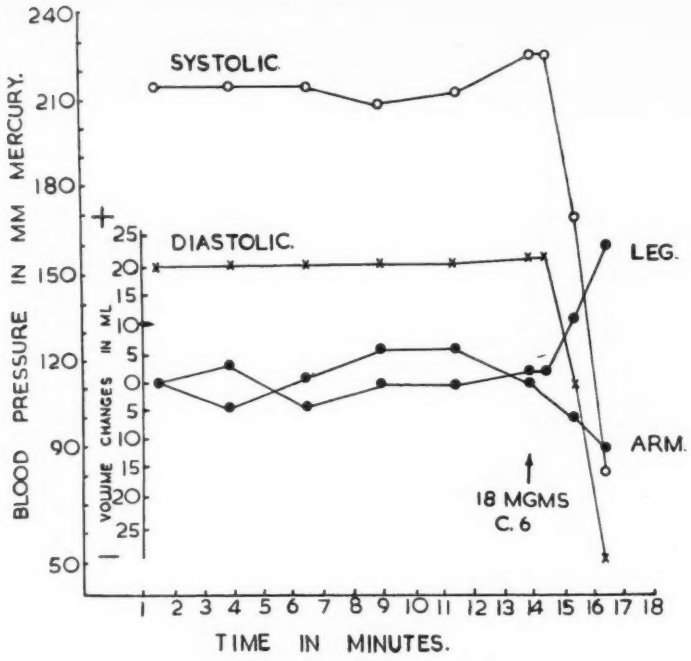

FIG. 2.—Effect of *H.M.B.* on limb volume.

postural hypotension after injections of H.M.B., though the extent of the blood pressure fall might be decreased by 30/10 *mm. Hg.*

This may be partly explained because at rest the pressure at any point in a vein or artery is equal to the general venous or arterial pressure plus the pressure of the column of blood extending vertically downwards from the angle of Louis to the point in the vessel under consideration. In the erect posture at rest it follows that the pressure in the veins at thigh level is less than the venous pressures near the ankle. Hence, if rubber bandages are applied with equal firmness to all parts of the legs, a degree of firmness that prevents over-filling of veins in the region of the ankle may obstruct the veins higher up.

That application of a uniform external pressure may actually prevent or delay the emptying of veins is readily seen in a simple mechanical model. A length of sausage skin, closed at one end, is tied on to a glass tube open at both ends. The sausage skin and the tube are filled with water and the skin suspended in the pressure bottle, the tube passing through a rubber stopper to the outside of the bottle. If the length of the sausage skin is 10 cm., the pressure of water within is a gradient between 0 at the top and 10 cm. H_2O at the bottom. If now air is introduced from a reservoir, so that the pressure in the bottle is raised, expulsion of the water in the sausage skin does not occur, even though the air pressure may be many times greater than the pressure of water at the bottom of the sausage skin. What happens is that the upper part of the skin is compressed whilst the lower part remains distended with fluid, which either does not empty or does so extremely slowly. If water instead of air is introduced into the bottle we provide an external counter-pressure which is graduated, being greater below than above. Then only a minimal excess of pressure is required to empty the sausage skin completely.

Effective neutralization of gravitational distension of blood vessels is probably best effected, therefore, by immersion in water, which provides a graduated external counter-pressure which is greater below than above. It was, therefore, decided to attempt to neutralize the postural hypotension by immersing the patient in a warmed swimming pool.

Effect of Immersion in Water Upon the Postural Hypotension Induced by Hexamethonium Bromide

Arrangements were made to have the water in the Physiotherapy Swimming Pool at 89° F. and the room temperature 83° F. Patients used to investigations were injected subcutaneously with sufficient *H.M.B.* to cause a substantial fall in the blood pressure. Preliminary readings were made in the horizontal and standing postures. The patients then advanced into the water and the relationship between the depth of immersion and the level of the blood pressure was determined. A typical result is shown in Fig. 3. Twelve such investigations were made. As the patient went deeper into the water the blood pressure rose to higher and higher levels until, when it was up to the chin, the blood pressure was only a little below that recorded before the administration of *H.M.B.* This return of the blood pressure almost to its original high level during immersion must be due to the counter-pressure of the water applied to the external surface of the body which neutralizes the gravitational increases of intravascular pressure that occurs in the legs on standing. When after *H.M.B.* injection the patient stands erect but out of the water, this gravitational increase causes distension of blood vessels (arterioles, capillaries and veins) in the lower part of the body and so a fall in blood pressure. This distension of blood vessels and the fall of blood pressure is prevented by immersion in water. Control tests made on the same patients without *H.M.B.* injections show little or no influence of water immersion upon the blood pressure level (Fig. 3).

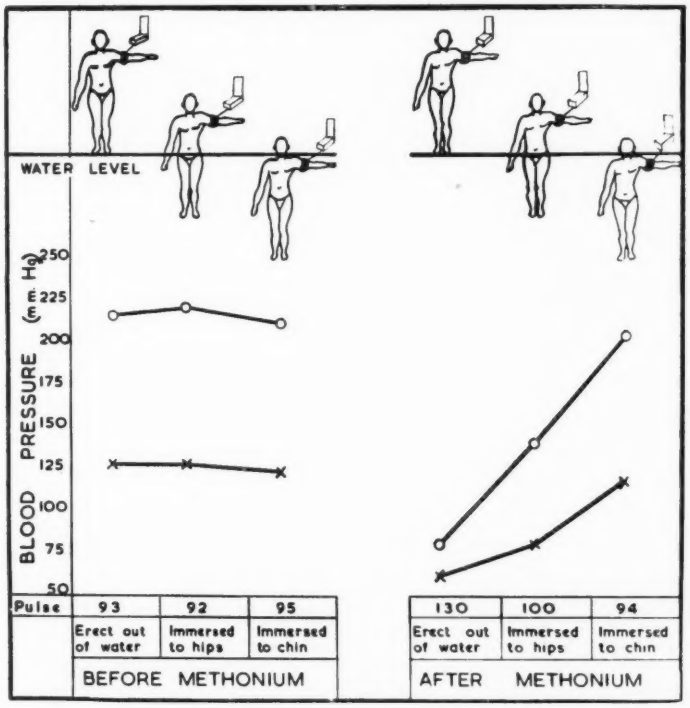

FIG. 3.—Effect upon the blood pressure of immersion of a patient to various depths in water, before and after injection of *H.M.B.*

After a suitable dose of P.M.B. or H.M.B. it is possible, by regulating the degree of immersion in warm water, to adjust the blood pressure of hypertensive patients at will to any desired level within a

range that may be as wide as 130 *mm. Hg systolic and* 50 *mm. diastolic. Such changes may be made in a few seconds, without symptoms, unless the pressure falls too low.*

As was anticipated, the blood pressure after *H.M.B.* was not significantly affected by posture so long as complete immersion was maintained. Any fall in pressure obtained with large doses, despite immersion, was the same horizontal or erect.

Evidence that Gravitational Effects Influence the Blood Pressure Levels in the Horizontal Posture after H.M.B.

After injections of *H.M.B.* observations were made in which the patient was supported on a canvas stretcher and blood pressures were measured. Maintaining the horizontal posture, the patient was lowered into a warm bath so as to be immersed, leaving only the nose and mouth above water, and the blood pressure measured again. The arm in which it was measured was held level with the anterior aspect of the thorax. It was higher when the patient was immersed in the water than when out of the water; when the patient was half immersed, the blood pressure assumed intermediate levels. It would appear, therefore, that some gravitational distension of blood vessels takes place even in the horizontal posture.

Such observations raised the question of whether almost the entire blood-pressure lowering effect of *H.M.B.* might depend upon loss of the ability to resist this gravitational distension of blood vessels.

It was decided to study the effects of water immersion with larger doses of *H.M.B.* A large hospital bath was filled with water at 38° or 39° C. Intramuscular injections of *H.M.B.* were given until there was a good fall of blood pressure even in the horizontal posture. The patient was lowered into the bath on a canvas support, maintaining the horizontal posture and leaving the mouth, nose, and forehead out of the water. The arm used for blood pressure measurement was inclined so that the antecubital fossa and half of the cuff were out of the water. In all 6 observations it was observed that after large doses of *H.M.B.* the blood pressure, although raised by immersing the patient in water, was not restored to the pre-injection level, often remaining 30–50 mm. in the systolic and 20 mm. in the diastolic below the pre-injection level (Fig. 6). *Blood pressure lowering by H.M.B. occurs even when gravitational increases in intravascular pressure of dependent blood vessels are counterbalanced by immersion in water. The water pressure will neutralize gravitational increases in intravascular pressure on both sides of the circulation.*

Effect of Water Immersion on the Postural Hypotension Following Surgical Sympathectomy

As the postural hypotension induced by injections of *H.M.B.* is thought to be due to blocking of sympathetic ganglia, it seemed of interest to consider the effect of an external counter-pressure on the postural hypotension that occurs after successful sympathectomy for hypertension.

Protocol—Surgical Sympathectomy. Mr. G. S., aged 49, essential hypertension, pre-operative pressure 210/145. Following sympathectomy (D.10 to L.2 inclusive) his blood pressures out of the water were: lying 168/102, standing 120/104. Walking into the warm swimming pool his blood pressures were: at hip level 158/114, and at chin level 170/120. As the subject left the water the blood pressure fell.

In a patient with naturally occurring postural hypotension we confirmed the observation of Stead and Ebert (1941) that the postural fall of blood pressure can be prevented by immersion in water.

Effect of Applying a Uniform Positive Pressure to the Body Surface Below Nipple Level

When the body below the nipple level is enclosed in an air pressure chamber it is possible to study the effect upon the hypotensive action of *H.M.B.* of applying a uniform external counter-pressure of 20–60 mm. Hg to those parts of the body that lie within the pressure chamber. Investigations were made with a patient in the upright posture so that on injection with *H.M.B.* the blood pressure fell to a low level. *It is clear that after H.M.B. the application of an external counter-pressure with compressed air may raise the blood pressure significantly, and may restore a patient who is feeling faint* (*Fig.* 4).

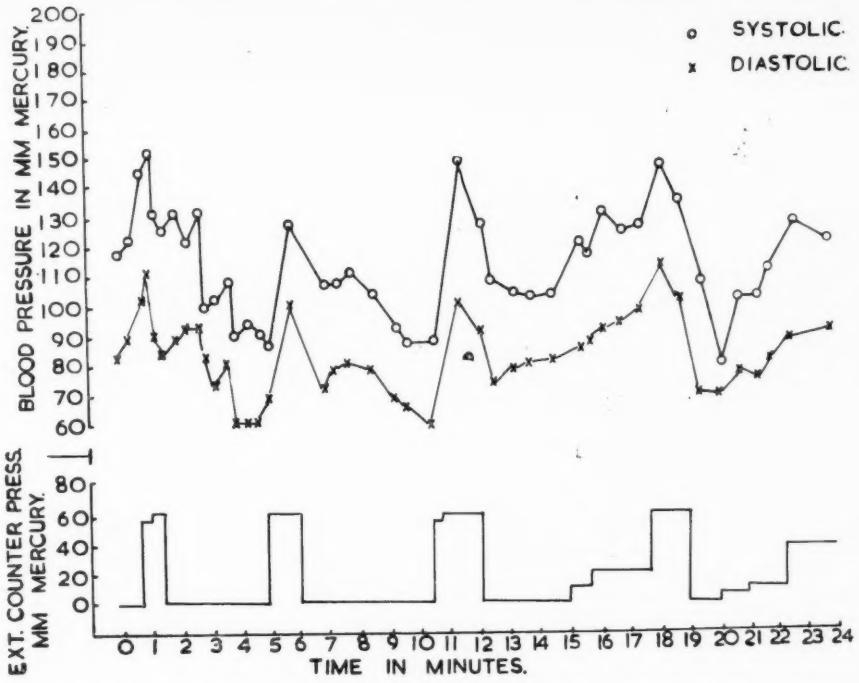

FIG. 4.—Effect of applying a positive air pressure to the body surface below the nipple level after an injection of *H.M.B.*

Effect of Applying a Uniform Negative Pressure to the Body Surface Below Nipple Level

When the body below nipple level is enclosed in a pressure chamber, the application of a negative pressure may reduce the blood pressure even when no *H.M.B.* has been administered (Fig. 5). The return of the pressure in the chamber to the atmospheric level is associated with restoration of the original blood pressure. After administration of *H.M.B.* the effect of a negative pressure applied to the lower two-thirds of the patient's body is greatly enhanced and, with sufficient negative pressure, a patient may be brought near to fainting within a few seconds. During the application of a negative pressure, either without or with the previous administration of *H.M.B.*, a distinct fall in the venous pressure was observed in the neck veins. *The fall of arterial pressure is greater after H.M.B., probably because arterioles, capillaries, and veins are less able to resist an expanding force.*

The effect of applying a negative pressure to the entire body is not the same. A hypertensive patient and an observer were enclosed in an Air Force decompression chamber and the pressure within the chamber reduced to 236 mm. Hg below atmospheric, corresponding to a height of 10,000 ft. As expected, there was no appreciable effect upon the blood pressure level.

Effect of Immersion in Water on the Blood Pressure Lowering Effect of Nitroglycerine

It is generally thought that nitroglycerine acts by direct depression of the smooth muscle of blood vessels. It has been pointed out by Weiss *et al.* (1937), that a degree of postural hypotension occurs during the action of nitroglycerine. It was, therefore, of interest to decide whether the fall of blood pressure from 1/200 or 1/100th grain of trinitrin, dissolved under the tongue, with the

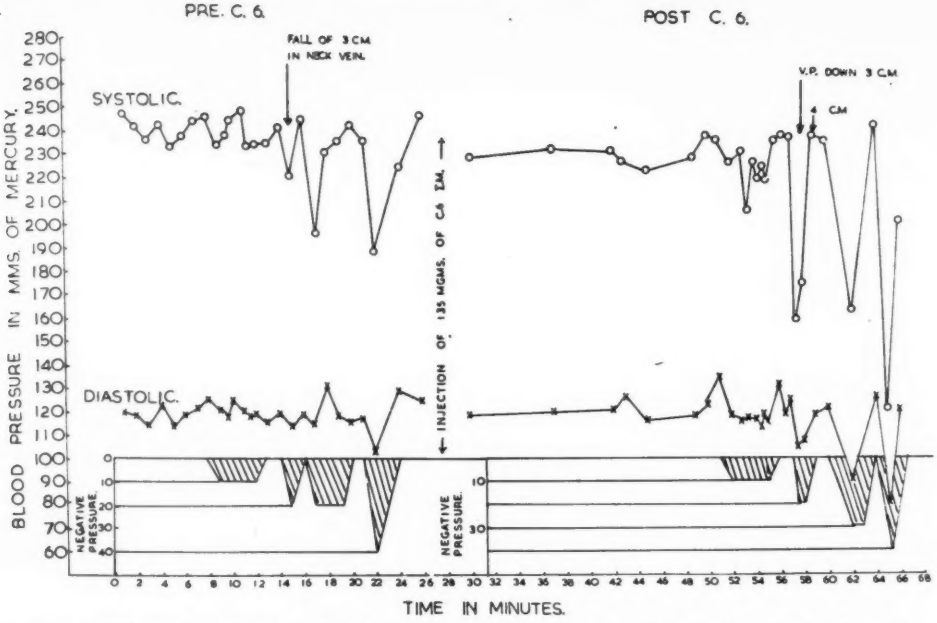

FIG. 5.—Effect of applying a negative air pressure to the body surface below the nipple level, before and after giving *H.M.B.* The degrees of negative air pressure are in mm. of mercury.

subject in the erect posture, could be counteracted by immersion in water. Four experiments were performed, of which one is illustrated in Fig. 7.

With the doses employed, the blood pressure scarcely fell when the subject was immersed up to the shoulders in a warm swimming bath, whereas standing by the side of the swimming bath the same dose dropped the blood pressure to a low level and in some cases the subject felt faint and had to be laid flat.

Some Effects of H.M.B. on the Blood Flow

It has already been stated by Kay and Smith (1950) that, even with the blood pressure reduced after *H.M.B.*, the skin temperature in the arms, and especially in the legs, may rise. This suggests some dilatation of the arterioles in the part showing a temperature increase.

In hypertensive patients it was found that forehead temperature tended to remain unaltered or fall, and arm and leg temperatures to remain unaltered or more usually to rise. As the blood pressure falls after *H.M.B.* it follows that, if the limb temperature does not fall with it, then the peripheral resistance in the limb must have been decreased.

Cardiac Output in Relation to Blood Pressure Lowering by H.M.B.

Some preliminary observations (Restall and Smirk, 1950) suggested, on the basis of ballistocardiograms, that during blood pressure reduction by *H.M.B.* the heart's output at rest might be either increased or diminished. It seemed of interest to consider whether the blood pressure fall would be maintained if the heart's output were increased. Ballistocardiograms were taken on a hypertensive patient while at rest in the sitting posture first before and then after performing an exercise suited to his physical capacity. Ordinarily exercise was the ascent of some 20 to 40 steps. The patient then received a suitable injection of *H.M.B.* and the observation was repeated. The

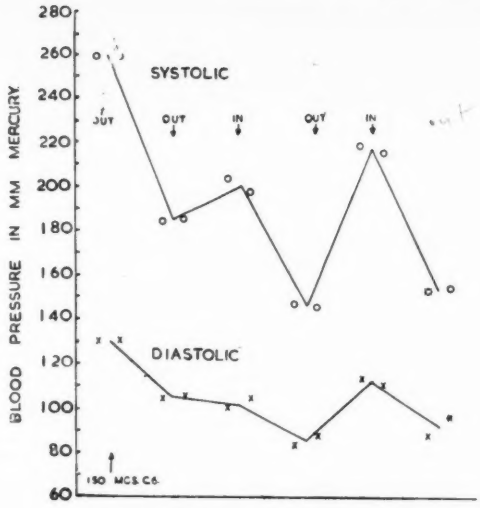

FIG. 6.—Effect of immersion in warm water on the blood pressure of a patient who is maintained in the horizontal posture throughout the test. The patient has received a subcutaneous injection of 150 mg. of *H.M.B.* (*In and out* refer to the presence or absence of water immersion at the time of measuring the blood pressure and an additional "out" should have been inserted above the last circle.)

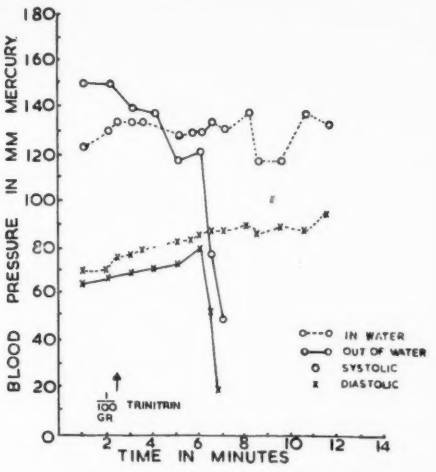

FIG. 7.—Effect of immersing the subject in water upon the hypotensive action of trinitrin.

blood pressure was measured at various stages in the course of the test. Four such experiments were performed.

Although ballistocardiograms may be open to suspicion as providing an absolute measurement of the cardiac output, there can be little doubt that gross changes in the cardiac output in the same subject can be reported on with some confidence. It will be seen that the increase of the cardiac output after exercise is not prevented by *H.M.B.* (Fig. 8), for both the rate of the heart and the amplitude of the deflections may be augmented simultaneously. *In the resting state immediately following exercise, and at a time when the cardiac output is increased, the blood pressure after H.M.B. remains at a low level.* On the basis of such results it is hoped in the discussion to comment upon the relationship between cardiac output and peripheral resistance.

DISCUSSION

When *P.M.B.* or *H.M.B.* are given in sufficient amounts they reduce the blood pressure even when the patient is in the horizontal posture. Their most prominent circulatory effect, however, is to induce a postural hypotension and as the subject approximates to the vertical the blood pressure falls further. The systolic fall is greater, the pulse usually accelerates and, with the patient sitting, the leg volume increases. Venous pressures fall, both in health and in congestive heart failure patients, and in 4 out of 5 of the latter a decrease in breathlessness occurred simultaneously.

An attempt to limit the postural blood pressure fall by elastic binding of the legs and abdomen led us to study the effect of a measurable hydrostatic counter-pressure obtained by immersing the patient in a warm swimming bath. The effects were dramatic, for as the patient walked on into the deeper part of the swimming pool so the blood pressure rose until, in some cases, it was only a little below the premedication hypertensive level. Rises of blood pressure of 130 systolic and 70 diastolic have been induced in this way, and by regulating the depth of immersion almost any

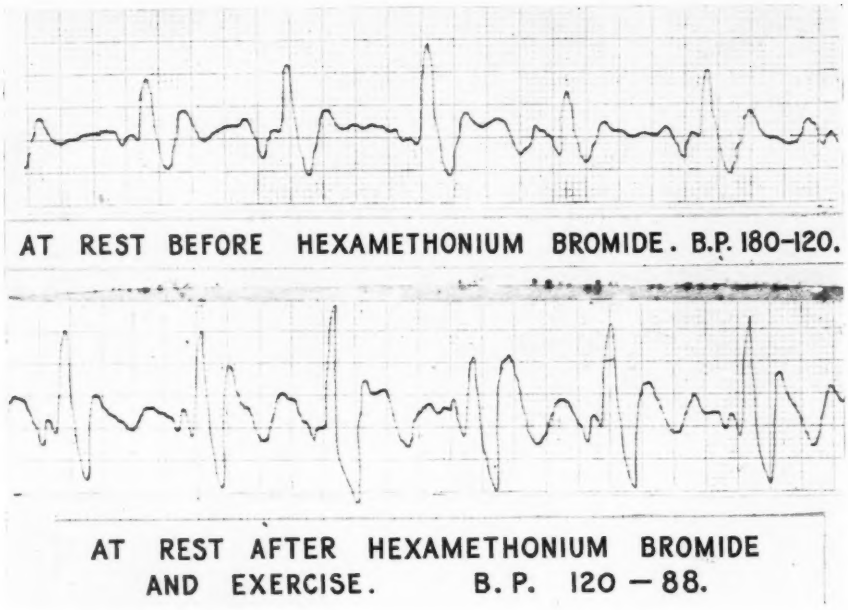

FIG. 8.—Ballistocardiographic evidence that blood pressure lowering from *H.M.B.* persists in the presence of a raised cardiac output. The blood pressure at rest was 180/120 before *H.M.B.*, and during rest after exercise was 120/88 after *H.M.B.* The corresponding ballistocardiograms are shown.

selected blood pressure within the range (either systolic or diastolic) can be obtained. If, before immersion, the pulse had accelerated as the blood pressure fell, then, on immersion, the pulse usually returned to its original rate as the blood pressure rose. Pulse rate is more closely related to blood pressure than to the amount of drug injected. In the swimming bath, as one might expect, there is practically no difference between a patient's pressure in the horizontal and in the vertical positions, provided that in both positions the patient is under water except for the parts above the level of the chin.

These investigations prompted others in which the patient stood in an air pressure chamber with an airtight joint at nipple level. It was found that a positive pressure applied to the body below the level of the nipples would partly counteract the hypotension that develops in the vertical posture after *H.M.B.* If, however, the device be used to impose a negative pressure upon the body below the nipple level then in normal and hypertensive people, even in the horizontal posture and without medication, considerable blood pressure reductions occur when the external pressure is reduced. A fall in venous pressure occurs concurrently. After administration of *H.M.B.* the effects are enhanced, bigger falls being obtained with lesser negative pressures. Negative pressure applied in this way is to some extent analogous to the effects of " G," as when an aircraft makes a sharp turn.

The great influence of posture on the blood pressure following *H.M.B.*, the nearly complete reversal of this effect by the external graduated counter-pressure of water, and the potentiation of the effect by a negative external pressure deserve an explanation. In our water immersion experiment the internal hydrostatic pressure on the venous side corresponds closely to the external counter-pressure of the surrounding water when immersion is to manubrial level (Smirk, 1936; Walker and Longland, 1950). We thought at first that the procedures described altered blood pressure by their effects on the amount of blood pooled in dependent parts, but later regarded their

effects on the calibre of arterioles, and hence on the peripheral resistance, as of greater importance. In perfusing isolated rat limbs we have noted that if the rate of perfusion is doubled the perfusion pressure is not doubled (cf. Poiseuille's Law). The reason is that the arterioles are stretched by the increased internal pressure leading to a decrease in peripheral resistance.

When a healthy man stands up there is a brief fall of blood pressure, probably due to distension of blood vessels following the gravitational increase of pressure within them. This quickly resumes its original level by reflex action through the carotid sinus and elsewhere. After *H.M.B.* the body loses some of its capacity to counteract this gravity-pressure dilatation of vessels because of the sympathetic paths having been made less effective. A similar loss occurs after nitroglycerine due to its direct inhibitory effect making the plain muscle less able to resist the rise of intravascular pressure. *So-called "postural hypotension" would be better termed "gravitational hypotension," since it can be shown to be present to some degree in the horizontal as well as in the vertical posture.*

Gravitational effects, though important, are not the whole explanation of the fall of blood pressure because sufficiently large doses of *H.M.B.* still cause distinctive blood pressure falls when gravity effects are counteracted by immersion in a warm bath. The effect of *H.M.B.*, decreasing the ability of vessel walls to withstand high intravascular pressures, probably explains why greater pressure falls occur when the initial pressure is high than when it is normal.

Confirming Kay and Smith (1950), we found that although the blood pressure falls after *H.M.B.* injections, the limb temperatures rise or are unaltered; hence the peripheral resistance in the limbs must be decreased. Evidently there is local arteriolar dilatation. Such local increase of blood flow may occur at the expense of other vascular beds, but a general increase requires increased cardiac output.

Under the varying conditions of everyday life ambulant patients, whether on *H.M.B.* treatment or not, exhibit changes in both cardiac output and peripheral resistance, and maintenance of a fall of blood pressure demands that the change in the relationship between them should be preserved under various physiological conditions. Were the blood pressure fall under *H.M.B.* dependent upon a simple change such as a decrease in the cardiac output, then the blood pressure should return to a high level if the cardiac output were raised by exercise. It has been shown that in a hypertensive under *H.M.B.* the cardiac output may be increased above the resting output by exercise without loss of the hypotensive action.

Conclusions

Hexamethonium bromide (*H.M.B.*) alters the relationship between cardiac output and peripheral resistance in such a way that, for any given cardiac output, the peripheral resistance is less than it would be in the absence of *H.M.B.* This altered relationship, though it may be modified, is not abolished by mild exercise, meals, and emotion.

The gravitational (so-called "postural") hypotension induced by *H.M.B.* is demonstrable in the horizontal as well as the vertical posture and is due to decrease in the capacity of vessel walls of dependent parts to contract and thereby resist gravity-pressure dilatation. This impaired homeostasis arises from less effective action of sympathetic paths.

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COMPLETE TRANSPOSITION OF THE GREAT VESSELS

BY

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In complete transposition of the great vessels the relative positions of aorta and pulmonary artery are reversed. Venous blood drains, as normally, into the right side of the heart but is returned immediately to the aorta: oxygenated blood passes from the pulmonary veins into the left side of the heart but is pumped through the pulmonary artery back to the lungs. The two circulations are independent and survival is possible only if other cardiac defects allow shunts of blood from each circuit to the other.

Such different views have been expressed recently about the diagnostic value of the X-ray silhouette, and about the prognosis that the time is ripe to attempt to explain and reconcile some of these differences. This paper is based on a study of 16 children with complete transposition: eleven were boys and five girls. The diagnosis has either been confirmed by necropsy or, in the surviving patients, is based on clinical and radiological evidence.

Incidence. Keith (1948) gives the incidence of complete transposition as about 10 per cent of all cases of congenital heart disease.

Of 300 children with congenital heart disease seen at the Birmingham Children's Hospital in eighteen months, 72 were cyanosed; 36 suffered from Fallot's tetralogy and 16 from complete transposition. This suggests the importance of the condition to the pædiatrician. During this same eighteen months, 24 cyanosed children died; 9 had complete transposition and 6 Fallot's tetralogy. Since there is such a difference in the prognosis of the two conditions and as only one is readily amenable to surgery, it is highly desirable that an accurate diagnosis should be made early in infancy.

Diagnosis: Clinical Picture

The symptoms and signs that we have found helpful in distinguishing transposition from Fallot's tetralogy are enumerated in Table I. Almost always cyanosis was noticed at the time of delivery;

TABLE I

Symptoms and Signs in 16 Cases of Complete Transposition

Cyanosis	16
Neonatal in all 16: differential in 1	
Dyspnœa	15
Paroxysmal in 3: with unconsciousness in 2	
Venous congestion	12
Cardiac enlargement	16
Absence of murmurs	7
Cough	7
Squatting	2

there was often difficulty in establishing respiration and five babies were thought in the first instance to be suffering from cerebral birth injury or pulmonary atelectasis. The onset of cyanosis might be delayed for a few hours. Its depth was increased by crying, coughing, or exposure to cold, and sometimes by feeding, and it is especially noteworthy that the child's colour improved very slowly,

or not at all, when oxygen was administered. Three patients who were severely cyanosed at birth later had such a good colour that they were thought to have uncomplicated septal defects. Emerson and Green (1942) mentioned that cyanosis might not be severe, and one of our children at the age of two years had a colour that was almost normal.

Tausigg (1947) pointed out that differential cyanosis, in which the lower part of the body is less deeply cyanosed than the upper part, is a sure sign of transposition. We have observed this phenomenon once. The infant died when only a few days old and, although the diagnosis is said to have been confirmed at necropsy, we have omitted the case from the series as it has been impossible to obtain adequate particulars.

Associated with the cyanosis there was moderate polycythæmia, averaging about 6·5 million red cells and 120 per cent hæmoglobin, and with a packed cell volume of 65 per cent. Clubbing was usually first seen at about the age of six months.

Panting was often a striking feature and has been noticed even in the youngest infants. Only twice was respiratory distress insufficient to excite comment, yet only three children have suffered from paroxysmal dyspnœa. About half the infants were difficult to feed and weight gain was nearly always slow. Development was delayed and activity severely limited, although one child was able to cover more than a mile if she walked slowly. The squatting or knee-elbow position was seldom effective in relieving respiratory distress.

Coughing was commoner than in Fallot's tetralogy. One child had anginal pain. Congestive cardiac failure was extremely common: distended neck veins and enlargement of the liver sometimes persisted for long periods with little change and digitalis was often needed; venesection helped one baby. Campbell and Suzman (1951) have commented on the frequency of distended veins in the fingers in cases of partial and complete transposition and we also have noticed this. Enlargement of the heart was difficult to recognize clinically during the first week of life, but quickly became obvious and a præcordial bulge sometimes developed. As in Fallot's tetralogy the second sound at the base varied greatly in quality and intensity. A thrill was unusual and nearly half the cases had no murmur. When present, murmurs were usually soft, systolic, and best heard in the third left space close to the sternum; but the majority of Mannheimer's (1949) cases had loud murmurs. In two children a diastolic murmur could be heard. " The sooner murmurs and thrills are disregarded the easier the diagnostic problem " (Taussig, 1947).

In summary, therefore, only one symptom can be regarded as diagnostic and that is the rare one of differential cyanosis of upper and lower extremities. However, as a means of distinguishing transposition from Fallot's tetralogy it is worth remembering that the colour and distress of infants with transposition are rarely improved either by placing them in the knee-elbow position or by administering oxygen. Coughing is often sufficient to excite comment, the heart is large, murmurs are frequently lacking, and chronic venous congestion is common.

Radiology

Contradictory views have been expressed about the radiographic appearance of complete transposition. Eek (1949) believes that, " As a rule the diagnosis is simple since the characteristic roentgen picture appears as early as the first months of life." On the other hand Castellanos *et al.* (1950) say: " The object of this investigation is to demonstrate that the cardiac outline has no value whatever in the diagnosis of transposition of the great vessels." Similarly Kerley (1951) says: " As the great vessels in infants cannot normally be identified there is little prospect of diagnosing these anomalies without angiocardiography."

According to Taussig (1947), the outstanding diagnostic feature is the narrow shadow cast by the great vessels in the frontal projection, with increase in width as the child is rotated into the left anterior oblique position. Frequently there is also a concave left middle cardiac segment, pulmonary congestion, and enlargement of both ventricles. Eek accepts the narrow vascular pedicle as the typical finding and describes a considerably enlarged heart as of a " characteristic egg-shape, with

the most pointed end corresponding to the apex in all cases." Campbell and Suzman (1951) commonly found a concavity in the pulmonary conus region, together with mottled lung fields, and dilated, pulsatile, pulmonary arteries. Wood (1950*a*) says simply that the diagnosis is usually easy and depends on " the recognition of pulmonary plethora in an obviously cyanotic child."

We cannot easily accept either of these extreme views. Although we do not believe that in infancy the diagnosis of complete transposition from direct X-rays and fluoroscopy is necessarily easy, we consider it is generally possible. Fig. 1 shows the cardiac silhouettes of 10 proved and 4 probable cases of complete transposition that were examined radiologically; further details are given in Table II. At first sight Castellanos's views seem to be justified. The shape of the heart in the different patients varies widely, sometimes even in the same individual at different ages. Cardiac enlargement may be of any degree and the heart may lie either transversely or obliquely. The heart shadow may extend some way or only slightly to the right of the spine, the left middle segment may

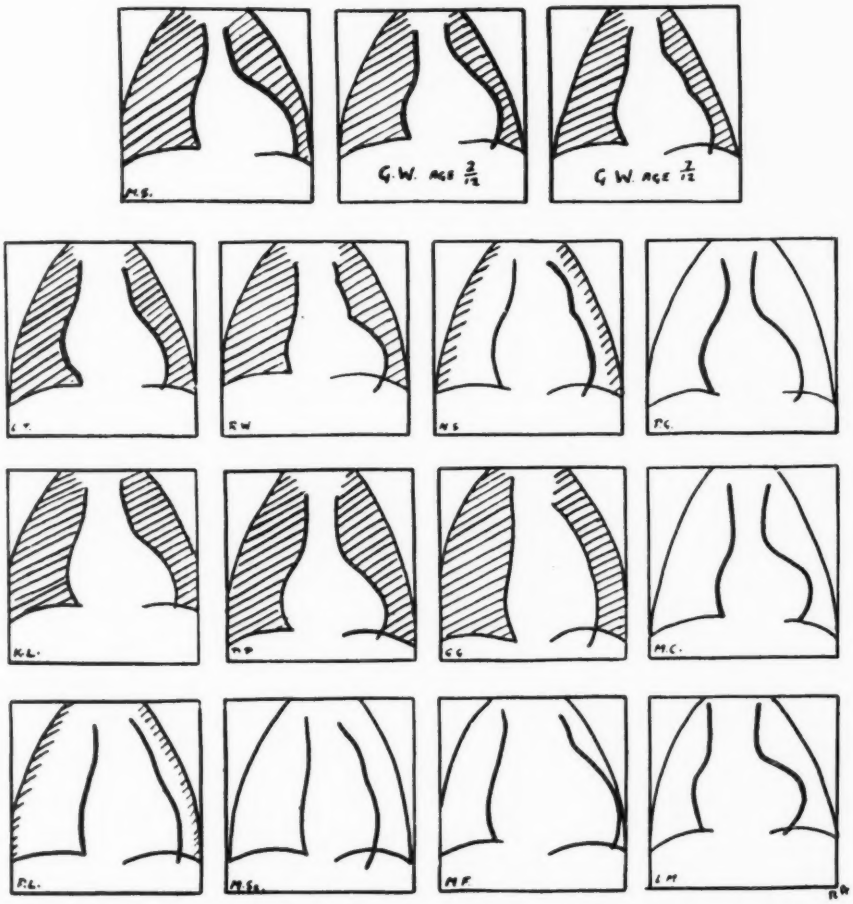


FIG. 1.—The cardiac silhouettes of 14 children with complete transposition of the great vessels. One child (G. W., top right) is shown twice, to demonstrate the variation of heart shape with age. (Shading indicates the presence of pulmonary congestion; partial shading means slight congestion and unshaded lungs are normal or oligæmic.)

TABLE II

RADIOLOGICAL FINDINGS IN 14 CHILDREN WITH COMPLETE TRANSPOSITION

Name	Age when examined	Lungs		Cardio-thoracic ratio	Extent of heart to R. of spine	Apex	Vascular pedicle	Left middle segment	Left anterior oblique view	Barium swallow*	Confirmatory evidence*
		Vascularity	Hilar pulsation								
M.C.	4 days	Normal to poor		61	Little	Elevated like Fallot	Narrow	Concave			P.M.*1
L.M.	2 weeks	Poor		58	Considerable	Elevated	Normal	Concave			P.M.*2
P.G.	4 weeks	Normal to poor	? absent	60	Considerable		Narrow	Concave	LV+	N	P.M.*3
M.F.	3 months	Poor		73	Considerable		Wide	Slightly prominent	LV+	N	
M.S.	9 months	++	++	65	Normal	Elevated	Very narrow	Concave	LV>RV	LA+*4	A., C. and P.M.*5
G.W.	10 months	++	+	67	Considerable		Normal	Prominent (flat at six weeks)	LV+, RV+	N.	A. and P.M. *6
P.L.	1 year	+		51	Little		Rather wide	Long, flat bulge	LV+	N.	A.*7
D.P.	1½ years	++		63	Considerable		Narrow	Concave			
N.S.	2 years	+		59	Considerable		Normal	Long, flat bulge	LV>RV	N.	A.*8
R.W.	3 years	++	++	58	Little		Normal	Slight bulge	LV>RV	N.	A.*9
L.T.	3 years	++	+	66	Considerable		Wide	Concave	RV>LV	N.	A., C. and P.M.*10
G.G.	4 years	++	+	57	Little		Wide	Long bulge	RV+	*11	
M.Sc.	4 years	Poor	Absent	47	Little		Normal	Very long and prominent	RV+	LA+*12	C. and O. *13
K.L.	5 years	++	+	53	Normal		Normal	Concave	LV>RV	N.	

* N=Normal, P.M.=Post-mortem examination, C=Cardiac catheterization, A=Angiocardiography, and O=Operation.

*1. *Necropsy:* Complete transposition. Pulmonary artery normal width. Right ventricle larger than left ventricle. No septal defects. Wide patent ductus.

*2. *Necropsy:* Complete transposition. Hypoplastic pulmonary artery. Large V.S.D.

*3. *Necropsy:* Complete transposition. Pulmonary artery normal width. No septal defects. Patent foramen ovale. Ductus closed.

*4. Extra impression on the anterior aspect of the barium-filled œsophagus, at the level of T.5, which slopes upwards from left to right.

*5. *Angiocardiogram: Type* 2. Aorta arises well to left, over outflow of right ventricle, ascends towards right and arches over left bronchus. High concentration in aorta: heart is empty in 2½ sec. No main pulmonary artery seen and little diodone in lungs. *Catheterization:* Equal saturations in right chambers. *Necropsy:* Complete transposition. Small high V.S.D.

*6. *Angiocardiogram: Type* 1. *AP.* Aorta from right ventricle near midline. High concentration in aorta but none in main pulmonary artery. Heart empty in 4½ sec. *LAO.* Right heart empties into aorta in 2 sec. Some diodone in left ventricle and right pulmonary artery in later films but no main pulmonary artery from right. *Necropsy:* Complete transposition. Aorta and pulmonary artery side by side. High V.S.D.

*7. *Angiocardiogram: Type* 2. Aorta arises well to left and constitutes left mid segment as it ascends to arch over left bronchus. No main pulmonary artery filling seen.

*8. *Angiocardiogram: Type* 2. Aorta arises well to left and constitutes left mid segment as it ascends to arch over left bronchus. High concentration in aorta: heart nearly empty at 2 sec; a little in lungs but no main pulmonary artery filling seen.

*9. *Angiocardiogram: Type* 2. Very similar to 8. Right chambers large.

*10. *Angiocardiogram: Type* 1. Aorta arises near midline, like Fallot. High concentration in aorta but main pulmonary artery filling not seen. Little in lungs. Heart empty in 3 sec. *Catheterization:* No left to right shunt but catheter thought to pass through V.S.D. *Necropsy:* Complete transposition. Septal defect between right ventricle and left *atrium.*

*11. Deep aortic impression on left lateral aspect of œsophagus.

*12. Extra impression of the left and anterior aspects of the barium-filled œsophagus, above the level of the aortic arch.

*13. *Catheterization:* Right ventricular pressure high. Shunt from left to right ventricle. *Thoracotomy:* Transposed aorta seen. Pulmonary stenosis.

be concave or convex, and the lungs may vary from a state of gross congestion to one of normal or deficient vascularity.

Yet there are three features that we consider important and if any one of these is found it strongly suggests the diagnosis of transposition.

(1) In 4 of the 14 cases the narrow vascular pedicle was seen.

(2) In 4 cases there was a long bulge of a special type in the left middle segment of the cardiac outline.

(3) In 4 patients a concave left middle segment was associated with pulmonary plethora.

A fourth feature may be mentioned. Pulmonary plethora occurring when there is neither a concave left middle segment, nor either of the first two signs, is suggestive of the diagnosis if the child is cyanosed. But it is not pathognomonic, for we have seen it in other conditions associated with cyanosis, e.g. persistent truncus arteriosus.

Table III analyses the cardiac silhouettes in terms of these four signs: 10 of the 14 children showed one or more of the three characteristic features and 2 of the 5 with pulmonary plethora without a pulmonary segment showed this without any of the other signs. In the remaining 2, there was no direct X-ray evidence of the transposition.

TABLE III

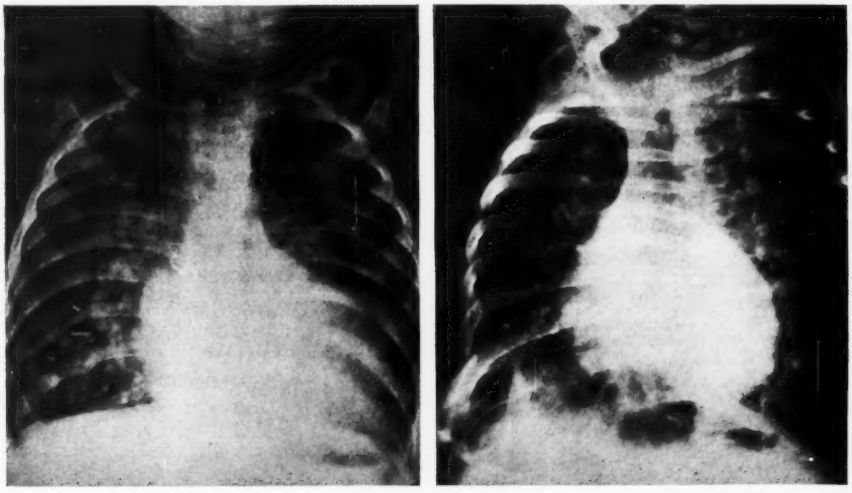
ANALYSIS OF THE X-RAY FINDINGS IN TERMS OF THE FOUR SIGNS DESCRIBED

Name	M.S.	D.P.	M.C.	P.G.	G.G.	N.S.	P.L.	M.Sc.	L.T.	K.L.	R.W.	G.W.	L.M.	M.F.
Narrow vascular pedicle ..	×	×	×	×										
Long, prominent left mid segment					×	×	×	×						
Pulmonary congestion plus concave left mid segment	×	×							×	×				
Pulmonary congestion without concave left mid segment					×	×	×				×	×		

N.B. Normal or oligæmic lungs were shown by 5 children; only two of these (M. Sc. and L. M.) had pulmonary stenosis.

(1) *The narrow vascular pedicle* (Fig. 2A) can be a very striking feature although, like Eek (1949) we found it difficult to recognize a widening of the vascular shadow in the left anterior oblique position (Fig. 2B). The sign is not pathognomonic unless the narrow segment is quite definite and extends over a considerable length of the superior mediastinum: if it is short it is unwise to make a firm diagnosis for it can occur in other conditions and we have been deceived by its presence in a baby who had pure pulmonary stenosis and died in heart failure with cyanosis.

(2) The second characteristic sign occurs *when the bulge of the transposed ascending aorta appears as the left middle segment* (Fig. 3). To distinguish this from a prominent pulmonary artery, the length and shape of the segment is important rather than the degree of protrusion. The bulge extends from the left ventricle as an almost smooth upward continuation of its curve and may reach nearly as high as the sterno-clavicular joints. Consequently it often occupies the position of both the normal pulmonary and aortic segments. Under the fluoroscope, aortic pulsation can be seen all along the curve. It must be distinguished from the thymus and from segmental lesions of the left upper lobe.



A B

FIG. 2 (A).—The narrow vascular pedicle. Note the associated concave left middle segment and the pulmonary congestion. (B) The same child in the left anterior oblique position. There is *no* widening of the vascular pedicle. False impression of left ventricular enlargement.

(3) The third characteristic sign, *the association of pulmonary plethora with a concave left middle segment*, is due to a misplaced pulmonary artery. The concavity cannot indicate a small pulmonary artery because the lungs are plethoric. The sign is often associated with a narrow vascular pedicle (Fig. 2A), but occurred twice as an isolated phenomenon. By itself (Fig. 4), it is not so reliable as either of the first two signs, for it may be found in such conditions as persistent truncus arteriosus.

With the above reservation, any one of the three signs strongly suggests the diagnosis and, in practice, it is usual to find more than one sign. The absence of pulmonary plethora does not exclude the diagnosis of transposition. In 5 of the 14 children there was no congestion; in two this was due to a complicating pulmonary stenosis but there was no stenosis in two (or possibly three) others.

FIG. 3.—The transposed ascending aorta may produce a long bulge in the left middle segment.

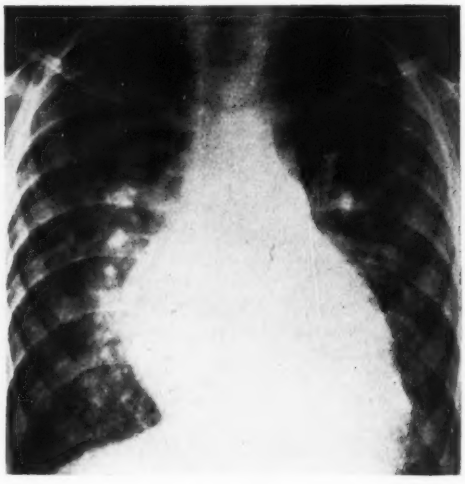


FIG. 4.—A concave left middle segment associated with pulmonary congestion may occur without the appearance of a narrow vascular pedicle.

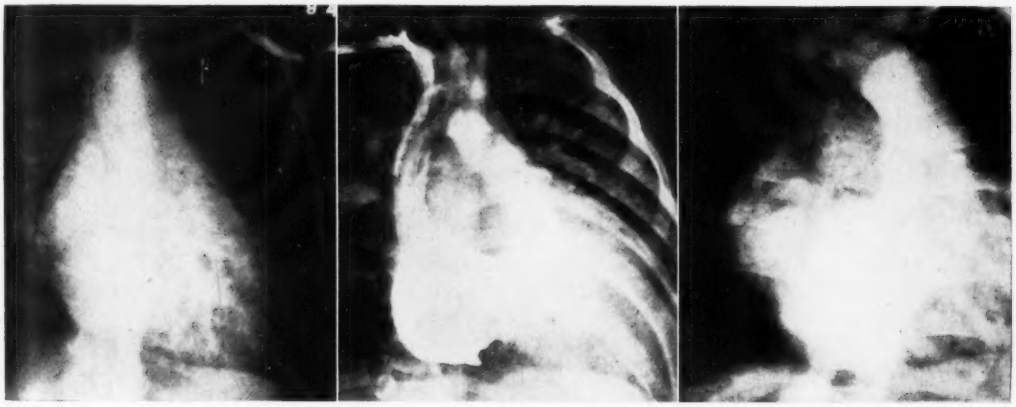
In the left anterior oblique position, backward projection is commonly greater than forward projection of the heart (Fig. 2B). Ordinarily this would indicate that the left ventricle is larger than the right. On one occasion the discrepancy was so great that we thought the child had tricuspid atresia and a non-functioning right ventricle. But, as Taussig (1947) points out, in transposition the aorta is displaced anteriorly so that a false indication of relative ventricular sizes is obtained and necropsy shows that the right ventricle is in fact the larger. Although left atrial enlargement has been demonstrated twice, we have failed, as a general rule, to recognize the atrial dilation that is so prominent a feature at necropsy. On two occasions there was in the barium-filled œsophagus an extra impression of the type seen with a left-sided origin of the right subclavian artery.

Differential diagnosis from Fallot's tetralogy is of great practical importance. It is relatively easy if the lungs are congested, but may be very difficult when a child with transposition has normal or decreased pulmonary vascularity. It should be pointed out that it is practically impossible to assess by fluoroscopy whether a *baby* has pulmonary plethora or oligæmia, and that good films are essential. When the pulmonary vessels are oligæmic, unmistakable narrowing of the vascular pedicle or recognition of a long aortic bulge in the left middle segment strongly favours a diagnosis of transposition; we have seen neither of these features in Fallot's tetralogy. Some assessment of the defects associated with complete transposition may be possible. Normal or oligæmic lungs

suggest either that the two circulations are mixing via the foramen ovale and a patent ductus or that there is a complicating pulmonary stenosis. In a child that has survived the first year of life the latter is more probable, while in such an older child congested lungs probably indicate a ventricular septal defect.

Angiocardiography has been used to confirm the diagnosis in 6 of the children. The main findings may be summarized as follows. From the right ventricle diodone passes immediately into the aorta, filling it and its branches in high concentration. The heart empties quickly (in two to five seconds), and little or no contrast medium can be identified in the left heart chambers. Despite pulmonary plethora little diodone reaches the lungs. Indeed, we have been unable to identify the pulmonary artery and its bifurcation in the frontal projection.

The origin and course of the aorta are variable. Castellanos *et al.* (1950) describe four different patterns, but we have divided our cases into two common varieties.



A B C

FIG. 5.—Angiocardiographic appearances in complete transposition. (A) *Type* 1. (The child shown in Fig. 4.) 2-second film. The aorta originates near the midline. (B) *Type* 2. (The child shown in Fig. 2A and B) 0·5-second film. The aorta originates to the left, from the outflow tract of the right ventricle. It ascends towards the right before arching over the left bronchus; hence it contributes little to the width of the superior mediastinum, which therefore appears narrow in Fig. 2A. (C) *Type* 2. Film at 1 second. The aorta ascends more vertically than in the previous example and produces a long bulge in the left middle segment, like that shown in Fig. 3.

Type 1. In 2 children the aorta arose near the midline and arched normally, as in Fallot's tetralogy (Fig. 5A). Campbell and Hills (1950) suggest that this indicates partial transposition, but in both of these children necropsy proved it to be complete.

Type 2. In 4 children the root of the aorta lay further to the left, in the position normally occupied by the main pulmonary artery (Fig. 5B and 5C). The aorta ran upwards and more or less obliquely to the right, and then arched over the left bronchus; occasionally it may cross the right bronchus (Castellanos *et al.*, 1950). Because this pattern is quite distinctive we consider that the anterior-posterior projection is the position of choice for angiocardiography when transposition is suspected.

It appears likely that the main difficulty in angiocardiographic diagnosis would be to distinguish Type 1 transposition, with poorly vascular lungs, from Fallot's tetralogy with pulmonary atresia. This problem has not yet confronted us. The course of the aorta explains the direct X-ray signs. Where, in Type 2 transposition, the aorta ascends almost vertically and runs only slightly towards the right, it forms the characteristic bulge on the left heart border (Fig. 5C).

Taussig explains the narrow vascular pedicle on the ground that the pulmonary artery, displaced

to the right, lies almost directly behind the aorta. This would account for Cases of Type 1 transposition with narrow great vessels but we have not seen this combination. We believe that the sign is seen in Type 2 when the ascending aorta takes a nearly horizontal course to the right and so contributes little to the width of the superior mediastinum (Fig. 2A and 5B).

Although we have observed no ill effects, angiocardiography in complete transposition is not without risk. Diodone enters the cerebral circulation in high concentration and Broman and Olsson (1949) have shown in the rabbit that this can upset cerebral vascular permeability. Apparently permanent disturbances of the electro-encephalogram have been observed and it is clearly important to establish a less hazardous method of diagnosis. Recognition of the direct radiographic appearances that we have described may reduce the need for angiocardiography, although we believe it justifiable when the diagnosis is in doubt.

Electrocardiography

The electrocardiographic picture is not specific and may be indistinguishable from that found in Fallot's tetralogy. The electrical axis shows considerable variation but usually lies within the range of right ventricular preponderance. Chest leads show that there is often clockwise rotation of the heart so that leads V2–V6 may lie over the epicardial surface of the right ventricle. Incomplete right bundle branch block has been seen once, in a patient thought to have a ventricular septal defect. Characteristically the P waves are tall and peaked in the standard limb leads, especially in lead II. This presumably reflects the considerable atrial dilation that is a feature of the condition.

Cardiac Catheterization

We have examined only three cases of transposition by right heart catheterization as we have found angiocardiography a more valuable diagnostic procedure when dealing with small cyanotic children. But, as Bing *et al.* (1947) have also pointed out, catheterization may help to distinguish the nature of associated defects. Left-to-right shunts through septal defects will raise the oxygen saturation of blood in the right side of the heart and it may be possible to pass the tip of the catheter through the defect, although this is often difficult in infants with such small veins that the catheter has to be introduced at the groin. For this reason we failed on one occasion to identify a ventricular septal defect (V.S.D.) that was subsequently disclosed at necropsy. In another child, what we had identified as a V.S.D. turned out to be a sinus between right ventricle and left atrium. In older patients it is easier to pass the catheter through the defect and onward into the pulmonary artery so that pressures in the various cavities may be compared. Right ventricular pressure is alway high. If there is a V.S.D. the pressure in the right ventricle tends to exceed that in the left and in these circumstances aortic pressure is higher than that in pulmonary artery (Wood, 1950). However, if there is pulmonary stenosis as well as a V.S.D., or if the ventricular septum is intact and circulation depends on a valvular foramen ovale and patent ductus arteriosus, then pressure in the left ventricle and pulmonary artery is likely to be higher than that of the right ventricle and aorta. Campbell and Suzman (1951) report left-to-right shunts through defects of the ventricular septum in 6 of their series; these cases were apparently not complicated by pulmonary stenosis, but may have been examples of incomplete transposition of the great vessels.

Oxygen saturation of blood in the right side of the heart is very low but corresponds closely to that in the brachial artery. It is to be presumed that in a child with transposition and a patent ductus the oxygen content of blood in the femoral artery will exceed that in the right brachial artery.

Prognosis

In a series of 123 cases Blalock and Hanlon (1950) found that the average age at death was only 19 months. If the six oldest patients were omitted from this series the average survival period was reduced to 5½ months. Taussig (1947) states that most of these infants die in the first few weeks

after birth and rarely live for more than 14 months. On the other hand, Campbell and Suzman (1950) believe that the outlook can be " . . . very different from Taussig's picture . . . with its gloomy prognosis," and consider that, if a septal defect allows sufficient mixing for an infant to survive a year, there is no reason why life should not continue for a considerable period. There are records of such patients attaining their twenties and one man lived until he was 56 years of age.

The fate of our patients is summarized in Fig. 6. Although the numbers are small, the diagram gives the impression that there are two groups of cases. There is one group with a high mortality in infancy, and another group of patients who, having survived this dangerous first year, continue a precarious and limited existence. Thus there is need for some means of deciding to which group an infant belongs. Further, if so many children escape early death and are condemned to be severely handicapped for months or years, some method of relieving their distress is urgently required.

Fig. 6 also summarizes the most important cardiac defect occurring in association with the transposition in each patient. It can be seen that the prognosis is poor when a patent ductus arteriosus (D) is the principal additional defect, for all these patients died shortly after birth. Children with an unspecified (S) or a proved atrial (A) or ventricular (V) septal defect usually have a better chance of survival, especially if the defect is associated with X-ray demonstration of plethoric lung vessels (X). The prognosis is much less satisfactory if the lungs are radiologically oligæmic (O).

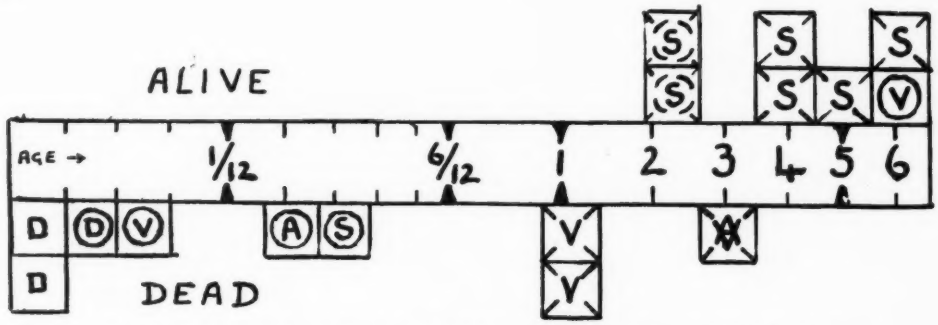


FIG. 6.—The ages and associated cardiac defects in our cases of transposition (See text).

Certain clinical and radiological features suggest that an infant has a patent ductus arteriosus and consequently indicate a poor prognosis. If the legs are consistently less cyanosed than the arms or torso, there can be no doubt about the diagnosis, but the sign is difficult to recognize. Marked venous engorgement in the neck and the development of generalized anasarca, together with radiologically clear lung fields, suggest a ductus rather than a septal defect. Rhythmic waxing and waning in the size of the right atrium is an X-ray sign described by Taussig that we have not yet seen.

We have failed to discover any clinical features that are certainly indicative of a septal defect and a relatively good prognosis. Children who had systolic murmurs also had septal defects but murmurs are notoriously misleading in this condition. We thought that a history of chronic cough or the finding of persistent rales might indicate pulmonary vascular congestion, but no such relationship could be established. X-ray evidence of pulmonary congestion is usual when there is a septal defect, but the combination is not invariable. Even cardiac catheterization sometimes fails to demonstrate a V.S.D. It seems to be easier to establish the case with the bad prognosis than to recognize the infant who will survive.

The frequency of venous congestion and the rarity of unconsciousness or fits suggest that death is more likely to result from myocardial failure than from cerebral anoxia. It is difficult to accept

Brown's (1950) explanation that the cardiac enlargement is just " a result of shunts through persistent orifices," for rapid and progressive enlargement does not occur in such defects uncomplicated by transposition. It seems likely that myocardial ischæmia is the important factor responsible for enlargement, and it may be significant in this connection that at least one child had angina of effort, and that a two-day-old child had thrombosis of a coronary artery. Further, microscopic examination of the myocardium always shows necrobiotic changes in the heart muscle with loss of striation, nuclear degeneration, and hyaline changes; destruction of muscle structure is often severe.

When both coronary arteries arise from the pulmonary artery, life cannot be sustained for more than a few days. Similarly, in transposition, if the coronary arteries are irrigated with venous blood a short life is to be expected. This happens when transposition occurs with an intact ventricular septum and a patent ductus arteriosus, for oxygenated blood can pour freely into the descending aorta but it can never reach the ascending aorta and the coronary arteries. Patients with a septal defect have a better prognosis because oxygenated blood can enter the right ventricle and so reach the ascending aorta and coronary arteries. The way in which this happens demands more detailed consideration.

Shunts in Transposition

There has been wide acceptance of Taussig's (1947) suggestion that, when a V.S.D. is the chief associated abnormality, blood passes to and fro through the gap, accumulating on each side in turn until the rise in pressure reverses the shunt. We find it difficult to accept this conception. Such an unstable system should tend to reach equilibrium and if it did not, the patient should have periodic variation in degrees of cyanosis and phasic variation in the shape of the T waves, neither of which we have observed. It is, however, a characteristic of these children that marked colour changes occur for no apparent reason even when the child is at rest. These changes were most marked in a child who had a large septal defect between the right ventricle and left atrium. In such a case, although there might be a flow from left to right in diastole or atrial systole, the maximal flow must have been constantly in the one direction, from right to left, during ventricular ejection. Taussig's contention that there is a " perpetual reversal in the direction of the shunt " is based on her observation of a periodic waxing and waning of the right atrium. But this is best seen when there is a valvular foramen ovale, an intact ventricular septum and a patent ductus arteriosus, circumstances in which, because of the valve, blood flow must be always from right to left atrium.

There are therefore grounds for believing that, in some cases at least, shunts in transposition are undirectional. We have investigated three varieties of shunt.

Type A Shunt. This is the shunt referred to above (a patent ductus arteriosus, an intact ventricular septum and a valvular foramen ovale). Pressure in the right atrium must exceed that in the left to ensure flow through the interatrial septum. On the other hand pressure in the pulmonary artery must be higher than that in the aorta so that blood can pass through the ductus into the descending aorta. This flow from the pulmonary artery into the aorta may account for the lack of pulmonary congestion that characterized our patients with this condition, while the high right atrial pressure may explain the systemic venous congestion and occasional œdema.

Type B Shunt. When transposition is combined with a V.S.D. we believe that the shunt is ordinarily from right to left ventricle. This suggestion is supported by some reports of pressure recordings (Wood, 1950*a*) but not by others (Campbell and Suzman, 1951). If the blood is being injected constantly into the pulmonary circulation as we believe, the smaller pulmonary branches will be congested, the pressure will rise and blood will be able to escape into the superior vena cava by way of the bronchial veins. That this happens is supported by the post-mortem finding of grossly congested lungs and Fig. 6 shows that, in all except three cases, children with septal defects had radiological evidence of vascular congestion in the lungs.

Type C Shunt. Three children with presumed ventricular septal defects had clear lung fields. At necropsy one was found to have a complicating pulmonary stenosis; in another no necropsy was allowed. The third child was shown by catheterization to have a shunt from left to right ventricle and at operation was seen to have pulmonary stenosis. In these cases oxygenated blood passes into the systemic circulation through the V.S.D. and back into the pulmonary circulation through the bronchial arteries or, if it is still open, the ductus arteriosus. Clinically, capillary congestion is systemic rather than pulmonary.

There are other varieties of shunt but we have had no opportunity to investigate them. Most important

of these is the association of transposition with a widely patent atrial septum. According to Wood (1950*b*) the shunt in such cases is from left to right atrium and blood presumably returns to the left side of the heart either through a V.S.D. or through the bronchial arteries. We have seen only one case of this kind and at necropsy this child was found to have wide bronchial arteries.

We cannot accept the view that congestion of the lungs in transposition is due solely to there being no obstruction to the flow of blood to the lungs. Undoubtedly the congestion is often a result of heart failure, but sometimes it may be an indication that blood can flow more readily from the systemic to the pulmonary circulation than it can in the reverse direction. If this be true, it will have some bearing on the design of operations for the relief of symptoms in transposition.

Treatment

Blalock and Hanlon (1950) discussed the various measures they have taken to relieve the symptoms of transposition. They pointed out that no obstruction exists in either circulation and that the problem is to transfer blood from each circuit to the other. The most successful operation was one that opened the right superior pulmonary vein into the right atrium, created an atrial septal defect and anastomosed the proximal end of a subclavian artery to the distal end of a pulmonary artery. Two-thirds of the children so treated survived and improved.

If our reasoning is correct it should be the first objective of operative treatment to increase the oxygen supply to the coronary arteries; hence the different types of shunt will require different treatment.

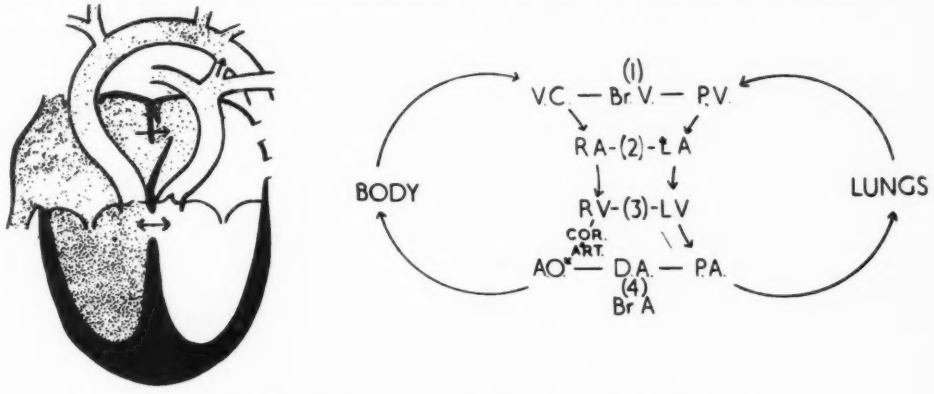


FIG. 7.—The circulatory route in complete transposition (See text).

Type A Shunt. Blood must necessarily pass from right to left through the valvular foramen ovale (No. 2 in Fig. 7). Oxygenated blood could best be diverted to the coronary arteries by creating a V.S.D. (3), if this operation were a less formidable undertaking. A less effective alternative would be to create a common arterial trunk by breaking down the aortic septum (4) as close to the coronary mouths as possible; the efficacy of the operation would be increased by closing the ductus arteriosus, providing of course that there were no break in the continuity of the aortic arch. Intervenous shunts (1) might be necessary as a final step to increase blood flow to the lungs; they could be produced between the right superior pulmonary vein and the superior vena cava, or by opening up the interatrial septum (Blalock and Hanlon, 1950). We have had no experience in the surgical treatment of this type.

Type B Shunt. Oxygenated blood reaches the right heart and the coronary arteries through the bronchial veins (1). This is a low pressure venous shunt, the efficiency of which could be improved by draining the right superior pulmonary vein into the right atrium (1) and by the creation of an atrial septal defect (2). Flow of blood from right to left could then be assured by joining the proximal end of a subclavian artery to the distal end of a pulmonary artery (Blalock and Hanlon, 1950). However, at the most oxygen would be obtained from only about a quarter of the available lung tissue. Despite this criticism, the operation has proved moderately successful in Blalock's hands and it is the best surgical procedure available for this form of shunt. Mr. A. L. d'Abreu has attempted the operation on two of our patients, both extremely ill. One

child died on the operating table. The other stood the operation well and his colour was strikingly improved, but shortly after he had returned to the ward respiration suddenly stopped; necropsy failed to disclose any reason for this unexpected death.

Type C Shunt. Blood from the left side of the heart reaches the coronary arteries by the most direct and effective route (3) but pulmonary stenosis reduces the flow of blood through the lungs. The creation of an artificial ductus (4) by a straightforward Blalock subclavian–pulmonary artery anastomosis would greatly increase the pulmonary blood flow and consequently would improve oxygenation of blood in the coronary arteries. Mr. d'Abreu has carried out this operation in one of our patients with such success that we have wondered whether it might not be advantageous to create an artificial stenosis of the pulmonary artery in cases with a patent ventricular septum. Blalock and Hanlon (1950) have had the same experience and have considered the same possibility.

None of the operative procedures suggested is entirely satisfactory. Unfortunately it is at present impossible to transfer the great arterial trunks to their proper ventricles because of the position of the coronary arteries. An alternative operation would be to transpose the great veins, draining all the pulmonary veins into the right atrium and the two venæ cavæ into the left atrium. The technical difficulties would be tremendous, but herein lies a challenge to surgical skill that surely will be accepted.

Summary

Transposition of the great vessels is second only to Fallot's tetralogy as a cause of cyanosis. The prognosis is poor, but a considerable number of children survive more than three years. Diagnostic features are reviewed in the light of 16 cases and new criteria are suggested for radiological diagnosis.

The importance of myocardial anoxæmia as a factor affecting prognosis is stressed and the theoretical aspects of operative treatment are considered.

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THE PATHOLOGY OF PULMONARY HEART DISEASE

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Right ventricular hypertrophy has been described in association with a variety of pulmonary disorders. In some of these there is an obvious relationship between the changes in the right ventricle and the severity of the pathological lesions in the pulmonary tissue, but in others it is difficult to find any correlation. The following review of the incidence of pulmonary heart disease in routine post-mortem material attempts to estimate the importance of some of the lesions of the pulmonary vascular tree as a morphological basis for the cardiac hypertrophy. Of 6770 necropsies available for study, 111 showed hypertrophy of the right ventricle secondary to disease of the lungs. In these cases any complicating factor such as essential hypertension, valvular lesions, or coronary vascular disease was excluded. The thickness of the ventricular wall was accepted as the index of hypertrophy, and while the ventricle was 5 mm. or more in thickness in all the cases studied, it was much more than this in the great majority.

The cases are classified according to their ætiology in the Table, where it is seen that in the material in this department emphysema is the most common cause. It is not intended to discuss all the various conditions listed, as similar analyses have been presented by Brenner (1935), Griggs *et al.* (1939), Scott and Garvin (1941), and Spain and Handler (1946). There are, however, certain subgroups that are of some interest because the absence of morphological lesions in the lung parenchyma suggests that the cause of the increased blood pressure is to be sought in the vascular tree itself. Such cases fall naturally into three groups.

Group I comprises those cases where there is an obvious obstructive lesion of the pulmonary vascular system to account for the changes in the heart, namely four of pulmonary arteritis, two of tumour embolism, and five of chronic pulmonary embolism.

Group II, the direct antithesis of Group I, consists of four cases where pulmonary hypertension or right ventricular hypertrophy occurs in the absence of any demonstrable histological lesion in the pulmonary vascular system. These constitute the " unknown cause " group or so-called primary pulmonary hypertension.

Group III includes 101 cases of emphysema, 39 with, and 62 without right heart ventricular hypertrophy. An additional 163 normal controls are included, to provide a study of the age changes within the pulmonary vascular system, and so to establish a standard of comparison for the influence of pulmonary disease in the genesis of sclerosis of the pulmonary vessels.

Group I. With Obstructive Pulmonary Vascular Lesion

Pulmonary Arteritis. Four cases of arteritis were found in this series. The ages of the patients concerned were 10, 13, 24, and 42 years. Three presented clinically with right heart failure of several months' duration and of obscure origin. Post mortem, an unexplained hypertrophy of the right ventricle was found, but on histological examination the large, medium, and small pulmonary vessels were the seat of an acute and healing arteritis, showing thrombosis, medial necrosis, and inflammatory infiltration going on to recanalization, scarring of the media and adventitial fibrosis (Fig. 1). The segmental scars in the media, from which elastic tissue was entirely absent, were very striking and such scars are regarded as characteristic of the healed stage of polyarteritis (Fig. 2). The pathogenesis of these cases is uncertain. On histological grounds alone the picture is identical with

TABLE

DISTRIBUTION OF INCIDENCE OF RIGHT VENTRICULAR HYPERTROPHY IN 6770 NECROPSIES

	Incidence	Cause of Death	
		Right heart failure	Other
Emphysema	39/101	20	19
Bronchiectasis	17/80	6	11
Asthma	14/24	9	5
Tuberculosis	7/92	3	4
Carnification	5/42	3	2
Embolism	5/103	4	1
Arteritis	4	4	—
Unknown cause ..	4	2	2
Primary carcinoma ..	3	—	3
Kyphoscoliosis ..	3	2	1
Secondary carcinoma ..	2	1	1
C. cystic disease ..	2	1	1
Fibrosis	2	—	2
Org. int. pneumonia ..	2	1	1
Asbestosis	1	—	1
Hæmosiderosis ..	1	1	—
Total	111	57	54

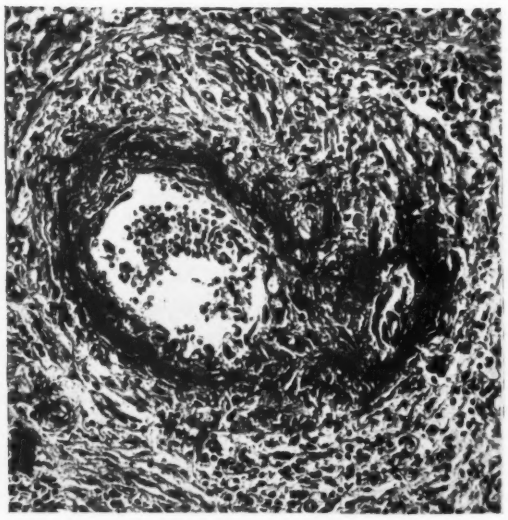

FIG. 1.—Pulmonary arteritis: vessel showing medial necrosis, and perivascular inflammatory infiltration (H.E., ×180).

FIG. 2.—Healed arteritis: pulmonary artery showing intimal fibrosis and elastic tissue defect in media (H.V.G., ×160).

polyarteritis nodosa when pulmonary involvement is only part of a widespread arteritis. It is difficult, however, to explain the localization of the lesion to the lungs, though some cases of polyarteritis nodosa do show an unusual restriction to certain sites. It may be that the lungs act as the " shock " organ, or that the nature of the allergen, its route of entry into the circulation, or the character of the " soil," or indeed all those factors that influence any hypersensitive reaction, modify the process so that only the pulmonary vascular system suffers.

The other alternative is that these cases of arteritis are examples of primary pulmonary hypertension, with secondary vascular necrosis, and that the condition is the counterpart of malignant hypertension in the greater circulation. The vascular changes, however, are not entirely comparable with those found in malignant hypertension, since all sizes of vessel are involved, intense inflammatory infiltration is a feature of the acute phase, the lesions are essentially segmental in character, and show a tendency to undergo healing. Furthermore, in this material vascular necrosis in the lungs in the

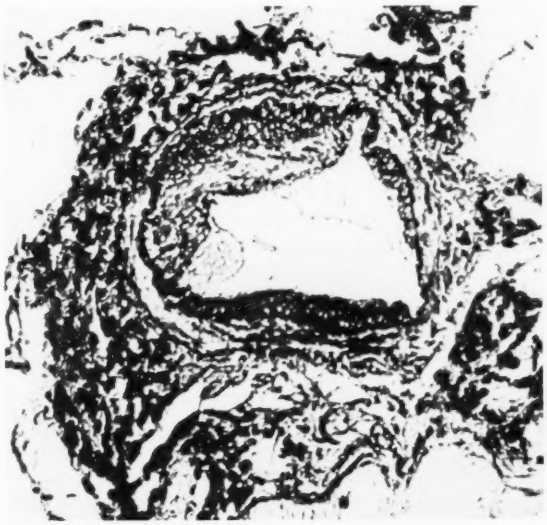

FIG. 3.—Pulmonary embolism: vessel showing organized thrombus, with reconstitution of the lumen and elastification of the intimal plaque (H.V.G., ×150).

presence of severe secondary pulmonary hypertension has not been noted; though Parker and Weiss (1936) describe necrotizing pulmonary arteriolitis in five cases of advanced mitral stenosis—lesions that resemble closely the vascular changes found in the kidneys in malignant hypertension, but not those described in these cases of arteritis. Appreciably higher pulmonary pressures have been recorded in cases of Eisenmenger's complex than in mitral stenosis, without the occurrence of vascular necrosis, but in this condition the adaptation of the pulmonary vasculature to abnormal pressure from birth and the development of marked vascular sclerosis probably protect the blood-vessels from the effects of extreme hypertension. One of the few references to pulmonary arteritis is in association with a case of Eisenmenger's complex described by Old and Russell (1950). The evidence available, therefore, tends to support the concept of a primary pulmonary arteritis rather than a vascular necrosis secondary to essential malignant pulmonary hypertension. Whatever the ætiology, the illustrations accompanying cases reported as examples of primary pulmonary vascular sclerosis make it apparent that some of them at least belong to this group.

Tumour Embolism. Two cases of tumour embolism with right heart hypertrophy were encountered. In one, symptoms of embarrassment of the right ventricle had been present for two years, the patient dying from right heart failure five years after removal of a uterine chorion-epithelioma. Post mortem, most of the large pulmonary vessels were filled with thrombus in which tumour cells were actively growing and invading their walls and then apparently undergoing arrest of growth, leaving vessels with medial scars devoid of elastic tissue, not unlike those seen in primary arteritis. Most cases of tumour embolism conform to the clinical picture of subacute cor pulmonale as described by Greenspan (1934) and Brill and Robertson (1937)—a right-sided hypertrophy occurring in association with diffuse carcinomatosis of the lungs, developing during the last few weeks of life. The unusual feature of this case, therefore, is the prolonged clinical course which is probably explained by the peculiar characteristic of the tumour in undergoing spontaneous regression after periods of active growth within the pulmonary vascular system.

The other case illustrates the second mechanism whereby tumour metastases may embarrass the right heart. A primary carcinoma of the œsophagus with extensive involvement of the pulmonary perivascular lymphatics had evoked a fibrous tissue reaction around the blood-vessels with secondary occlusion of their lumina. This type of secondary endolymphatic carcinomatosis is the commonest cause of subacute cor pulmonale.

Chronic Pulmonary Embolism. The present analysis revealed five cases of chronic pulmonary embolism with right ventricular hypertrophy, four of these dying from right heart failure. The duration of symptoms varied from a period of months to five years. Such a prolonged course, however, is not unique, since in a case mentioned by Castlemann and Bland (1946) there was a nine years' history of heart failure. One case showed almost complete and long-standing occlusion of both main pulmonary arteries and their branches, serving to illustrate the great reserve power of the pulmonary vascular bed. When recurrent pulmonary embolism has been present for some time it may present certain difficulties in histological interpretation, for the organization of emboli in the vessels leads to the formation of intimal thickenings which undergo elastification and are almost identical with those found in pulmonary arteriosclerosis (Fig. 3). This has been pointed out by Duguid (1946) who suggested that intimal plaques in the coronary vessels and aorta may be the result of organized thrombi and may be indistinguishable from arteriosclerosis. Harrison (1948) in a study of experimentally produced embolism traced the development of a fibro-elastic intimal plaque with reconstitution of the lumen in vessels the seat of previous embolism. Saphir (1947), too, has shown that even tumour emboli may undergo the same fate. Since, therefore, minor degrees of chronic pulmonary embolism are not uncommon, and fibro-elastic intimal plaques can evolve on this basis, care must be taken in the interpretation of sclerotic lesions of the pulmonary vessels. Some of the recorded cases of so-called primary pulmonary vascular sclerosis also may be explained in this way.

Group II. Primary Pulmonary Hypertension

In the second group of cases there were four in which right ventricular hypertrophy occurred in the absence of any morphological lesion that could be demonstrated in the pulmonary vasculature or parenchyma. These are regarded as examples of primary pulmonary hypertension. There is some confusion as to what constitutes primary pulmonary hypertension. It is attributed by Gilmour and Evans (1946) to a variety of pathological processes in the pulmonary vascular tree in the absence of any known cardiac or pulmonary disorder or any extrinsic disease capable of damaging the pulmonary vascular system: by certain standards this might be considered as a variety of secondary pulmonary hypertension. On the other hand, East (1940) suggests that in idiopathic or essential pulmonary hypertension there is little or no vascular change to which the right ventricular hypertrophy and failure may be attributed. The cases under consideration conform to this classification. De Navasquez (1940) discusses the condition as one of right ventricular hypertrophy of unknown origin, and presents three cases similar to those in this series: he questions whether the hypertrophy of the right ventricle justifies the opinion that it is due to increased work and

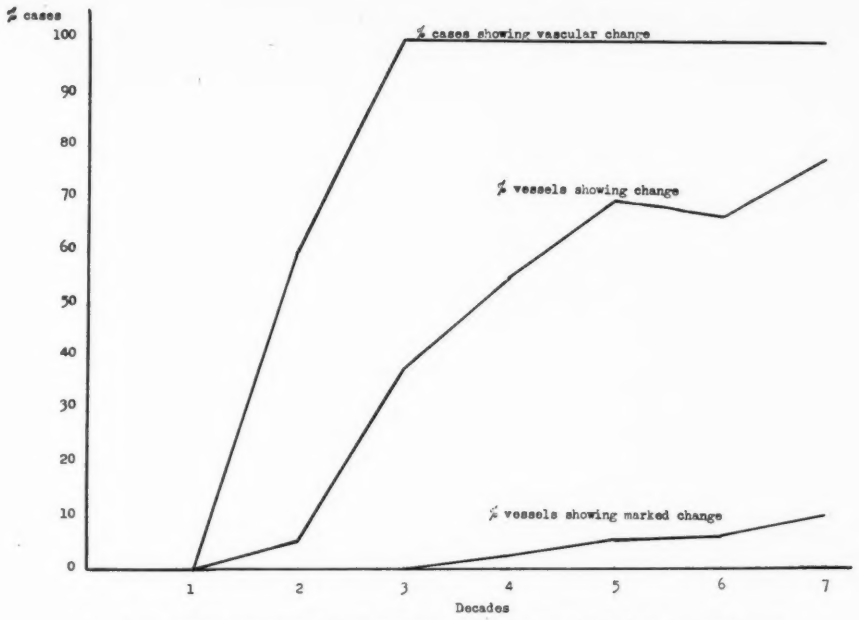

FIG. 4.—Graph showing incidence and extent of vascular sclerosis in control group.

analogous to left ventricular hypertrophy in systemic hypertension; and since no comparable lesion is found in the pulmonary blood-vessels he believes the existence of pulmonary hypertension is conjectural, and that idiopathic right ventricular hypertrophy would be a better name. It is well known, however, that changes in the systemic vessels are not invariably present in hypertension and are generally regarded as secondary to the hypertension. Since, also, the structure of the pulmonary arterioles differs from that of the systemic vessels, the failure to show hyaline arteriolosclerosis does not indicate that hypertension is not present. The condition may be analogous to systemic hypertension and perhaps initiated by a humoral or neurogenic mechanism. That such exists in the experimental animal has been shown by Daly *et al.* (1947) who demonstrated a vasomotor mechanism in dogs capable of causing a rise in pulmonary blood pressure. As it appears, therefore, from a study of this group of cases, that right ventricular hypertrophy can occur in the absence of any morphological change in the pulmonary blood-vessels, it is evident that too facile a correlation between pulmonary vascular lesions and changes in the right heart should be avoided.

GROUP III. EMPHYSEMA

There were 39 cases of emphysema with right ventricular hypertrophy, 20 dying of right heart failure. The importance of emphysema in the production of pulmonary vascular sclerosis is disputed, and sometimes an attempt is made to correlate the degree of vascular change with the presence or absence of right ventricular hypertrophy. Karsner (1933) considered emphysema to be the most important pulmonary condition in the genesis of arteriosclerosis of the pulmonary vascular system. Parker (1940), however, found pulmonary vascular changes in 80 per cent of 32 cases of emphysema, but concluded that there was no causal relationship between this change and the hypertrophy of the right ventricle. Evans (1951) has suggested that in conditions such as emphysema which may produce a slight rise in pulmonary pressure, hypoplastic changes in the vascular media under the

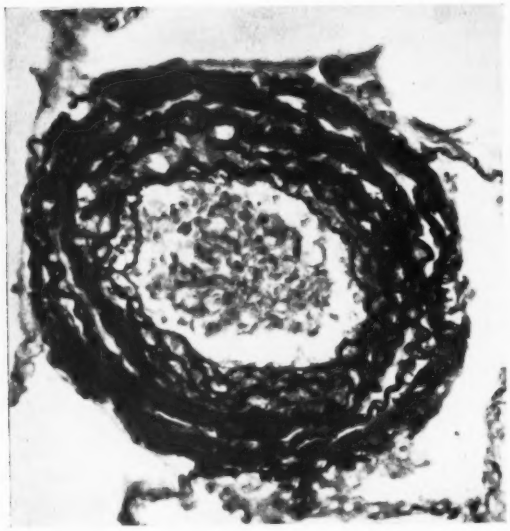

FIG. 5.—Control group: vessel showing marked intimal musculo-elastic hyperplasia (H.V.G., ×406).

FIG. 6.—Emphysema: vessel showing musculo-elastic thickening of the intima (H.V.G., ×406).

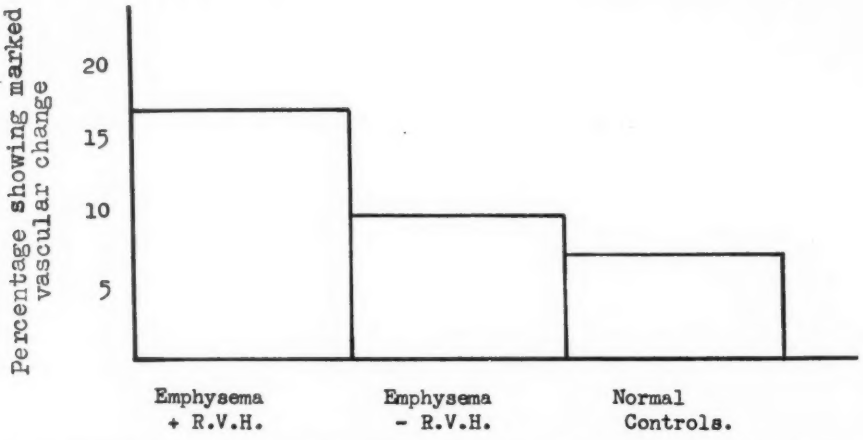

FIG. 7.—Shows incidence of marked pulmonary vascular sclerosis in emphysema compared with normal controls of similar age distribution.

stress of mild hypertension might lead to excessive compensatory endarteritis and eventually result in serious pulmonary hypertension. Before the significance of vascular changes in the lungs in emphysema can be correctly assessed it is essential to establish in control material the frequency and extent of sclerosis of the pulmonary vessels at all ages, but especially in the later decades. Only in this way can standards of normality be created against which the influence of conditions like emphysema can be compared. Brenner (1935) found that sclerosis was present in 97 per cent of

100 consecutive necropsies. Welch and Kinney (1948) described some degree of arteriosclerosis in every case from the fourth decade on. Civin and Edwards (1951) studied the changes in the different decades, and found them constantly present, but only exceptionally were they of such a degree as to narrow the lumen to any appreciable extent. Similar studies have been carried out in this department by Dr. R. A. Neely, in an analysis of 63 cases representative of seven decades, and carefully selected to exclude those with chronic disease of the heart or lungs. The changes found included varying degrees of intimal thickening due to fibro-elastic or musculo-elastic intimal hyperplasia, and affected all sizes of vessels to some extent. As representative of the whole group the incidence and severity of the lesions in the small arteries are presented in Fig. 4, and it is seen that in the later decades sclerosis is consistently present, and that in a small percentage of cases the degree of vascular change is marked. An example of such sclerosis is shown in Fig. 5, and can be compared with Fig. 6, which shows a similar degree of intimal hyperplasia in a case of emphysema. The incidence of vascular change in a further 100 control cases selected from the fourth to the seventh decade was compared with its frequency in the 39 cases of emphysema with, and in 62 cases of emphysema without right ventricular hypertrophy. The results are seen in Fig. 7. Taken as a whole, the incidence of severe sclerosis in these three groups shows little significant difference, 7 per cent in controls, 10 per cent in emphysema without right ventricular hypertrophy, and 17 per cent in emphysema with enlargement of the right ventricle. Since such a degree of vascular change occurs in controls without hypertrophy of the right ventricle and is absent in 83 per cent of cases of emphysema with right ventricular hypertrophy it cannot be regarded as a morphological basis for the hypertension. The most that can be concluded from this study is that emphysema accentuates slightly the normal age changes found in the pulmonary circulation. The reason, therefore, why some patients with emphysema develop right ventricular hypertrophy is not to be found in a study of the changes in the small vessels. The whole problem of right heart hypertrophy in emphysema is complex, and from the histological standpoint there is no constant pathological change found that might be regarded as a morphological basis for its development. One important factor is probably the reduction of the pulmonary reserve by gradual obliteration of the capillary bed. It is suggested by Spain and Handler (1946) that the resistance to flow is not necessarily based solely on the anatomical obliteration of the vascular bed, but in addition there is a functional pressure resistance relation occurring in functioning pulmonary tissue as exerted over a long period. Other factors of doubtful significance are diffuse fibrosis, polycythæmia, overfilling of the heart, increased cardiac output, and the existence of vascular shunts. In view of the different pressure relationships in the pulmonary and bronchial circulation, and the relatively small size of the bronchial arteries it is difficult to imagine how vascular shunts could play an important part in the prevention or production of pulmonary hypertension. It has been suggested that anoxia is an important factor in raising the pulmonary blood pressure, but conflicting results have been obtained in emphysematous patients in attempts to find a correlation between the arterial pulmonary pressure and the degree of arterial oxygen saturation.

Whatever the factors concerned, it is only the purpose of this paper to stress the almost constant occurrence of some degree of pulmonary vascular sclerosis in normal control material in the later decades. This observation should be borne in mind not only in the interpretation of vascular lesions in association with emphysema, but in any consideration of a possible morphological basis for pulmonary hypertension.

Summary

An analysis is presented of the incidence in 6770 necropsies of right ventricular hypertrophy in association with pulmonary disease. Three groups of cases are discussed in some detail. Group I comprises those cases where there is an obvious obstructive lesion of the pulmonary vascular system namely arteritis, tumour embolism, and chronic pulmonary embolism.

Group II consists of four cases of so-called primary pulmonary hypertension, where hypertrophy of the right ventricle occurs in the absence of any demonstrable lesion in the pulmonary vasculature or parenchyma.

Group III includes all the cases of emphysema, with or without right ventricular hypertrophy.

Though attempts have been made to correlate the right ventricular hypertrophy with vascular lesions in the lungs, it is shown that such lesions as are found in the small vessels conform to the normal age changes of the pulmonary vascular system, and therefore cannot be regarded as the morphological basis for the enlargement of the right heart.

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ELECTROKYMOGRAPHY—PRELIMINARY STUDIES

BY

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The study of the movement of the heart and great vessels by roentgenkymography suffered from the beginning in that tracings obtained by this technique did not permit of detailed analysis. Stumpf (1934) recognized this defect and attempted to overcome it by a technique called densography. By the use of a photoelectric cell with the property of varying its resistance in response to alterations in light intensity, he obtained tracings capable of linear magnification and detailed study. A similar principle is embodied in the electrokymograph which has been developed by Henny *et al.* (1947). Several groups of workers in the U.S.A. have published observations on heart and great vessel movement in normal and abnormal subjects, but so far, from this country, there has only been the one short communication by Wells (1950). The technical aspects of electrokymography have been described by Luisada *et al.* (1948). In the simplest terms the movement of the cardiovascular silhouette affects the amount of light falling on a phototube slit placed perpendicular to the cardiovascular border under fluoroscopic control, and the variation in light intensity is translated into a linear tracing. The polarity of the apparatus is arranged so that an increase in light causes a downward movement in the tracing. This may be produced by an inward movement of the cardiac border or by a decrease in the density of that part of the heart lying in front of the slit.

Various methods have been used to determine time relations; Henny and Boone (1947) employed the carotid pulse as a timing device, Luisada, Fleischner, and Rappaport (1948, 1949) the heart sounds, while Anderson (1948) and Lian and Minot (1946) used the electrocardiogram. More recently Mednick *et al.* (1950) have been employing two electrokymographs with simultaneous recording of the carotid pulse while Akman *et al.* (1950) has been using electrocardiograms with pressure pulses from the right ventricle and pulmonary artery.

METHOD

The Sanborn electrokymograph employed in this study is essentially similar to that developed by Henny and Boone and modified by Luisada and Rappaport. Electrocardiographic tracings and heart sounds have been recorded simultaneously using a Sanborn 4-channel poly-viso direct writing apparatus. In view of the limited linear frequency response of this recorder (80 cycles/second) the phonocardiogram does not record the heart sounds faithfully and has been used only for approximate timing while the electrocardiogram has been used in the detailed analysis of time relations. It is difficult to compare the relative amplitude of tracings from different parts of the cardiovascular border with this method, which is in this respect inferior to multiple-slit roentgenkymography.

Our records have been obtained with subjects standing behind a fluorescent screen in the postero-anterior and various oblique positions, and standard limb leads I and II are usually recorded. In order to obtain satisfactory cardiograms the subject has to be fully relaxed and the apparatus must be adequately earthed. The phonocardiograph microphone is placed over the base of the heart but has to be removed for the recording of aortic and some pulmonary artery tracings. The screening

current used is 4·5 mA. at 70 kVp. The whole procedure takes twenty to thirty minutes; the irradiation dosage received by subject and operators has been found to fall well within the limits of safety. The paper speed used routinely has been 25 mm. a second (normal electrocardiographic recording speed). The recording fidelity of the electrokymograph has been studied by Zinsser *et al.* (1950) and the time lag is about 0·015 to 0·025 second.

A common artefact noted was rounding or flattening of the top or bottom of the tracings. In most instances this was due to an unsatisfactory position of the slit so that the heart border moved across and then beyond it. It was commonly found in subjects with very forcibly acting hearts. We believe that these artefacts have not been fully recognized as such by some workers since certain published tracings include them without comment (Fig. 1).

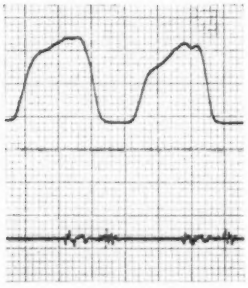


FIG. 1.—Electrokymogram taken from the lowest left heart border position (LV1) in a healthy male subject aged 18 years. The flattened trough of the tracing shows that in systole the heart border moves across and then beyond the slit.

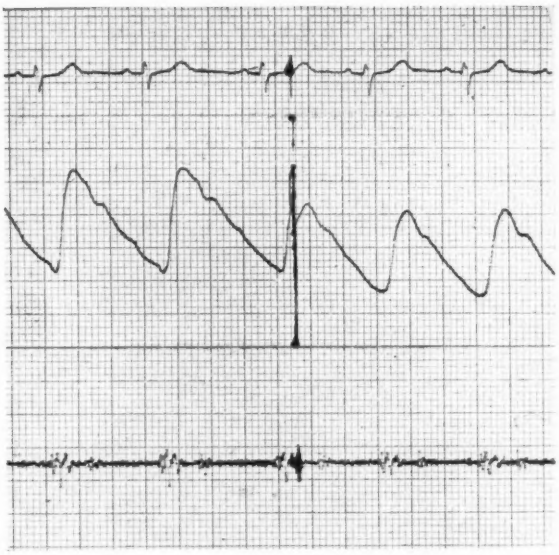


FIG. 2.—Electrokymograms recorded (1) from pulmonary artery and (2) from the aortic knuckle in a healthy woman aged 29 years. Note the resemblance to arterial pulse tracings and the accuracy with which filling can be timed from the electrocardiogram tracing above (standard limb lead 1).

MATERIAL

Normal Subjects. We have recorded electrokymograms from fifty normal subjects but as our technique has improved during this time we have selected only the last thirty for analysis.

These subjects were men and women medical students or ambulant patients from the surgical wards. Their ages ranged from eighteen to sixty years; there were nineteen men and eleven women.

Arterial Tracings. Electrokymograms recorded over the pulmonary artery and aorta showed a very close resemblance to arterial pulse tracings (Fig. 2). The dicrotic notch was usually more conspicuous in the pulmonary artery than in the aortic tracings.

Pulmonary Artery. Satisfactory tracings from the pulmonary artery were obtained in all thirty subjects, but in one the onset of the main upward deflection was slightly slurred rendering the tracing unsuitable for timing. In nineteen subjects consecutive complexes recorded showed a variation of not more than 0·01 sec. between Q and the onset of pulmonary artery filling in at least three

(usually four or more) complexes. In the remaining ten subjects the variation has been about 0·02 sec.

The interval from the onset of QRS to the onset of pulmonary artery filling varied from 0·08 sec. to 0·16 sec. In seventeen out of thirty subjects the interval was between 0·11 sec. and 0·13 sec. and in twenty-seven out of thirty between 0·10 sec. and 0·14 sec. This time interval has been studied by Richards *et al.* (1947) using a cardiac catheter passed into the pulmonary artery to measure the onset of filling (average 0·085 sec. with a range of 0·04 sec.), compared with our finding of 0·12 sec. with a range of 0·04 sec. in twenty-seven out of thirty subjects. Their findings of the relation between the onset of the P wave and the onset of auricular filling using the same technique agree closely with the previous findings of Lewis (1920) using the " a " wave in the jugular pulse tracing, when allowance is made for the inherent lag in their respective methods. Our findings would appear to indicate that there is an unexplained lag of about 0·035 sec. (Our figures have already been corrected for the instrumental time lag.) Catheter tracings are recorded from within the main pulmonary artery while electrokymograph tracings are taken from the cardiovascular border (possibly left pulmonary artery) but it is difficult to see how this short distance can account for the discrepancy. This problem is being studied further.

Aorta. Satisfactory tracings were taken from the aortic knuckle in twenty-nine of the thirty subjects. The time relations correspond closely with those obtained from the pulmonary artery.

Left Ventricular Tracings. Tracings were taken just above the diaphragm and at regular intervals up the left heart border. In subjects with vertical hearts three or four left ventricular tracings were obtained in the postero-anterior position; in subjects with horizontal hearts only two separate left ventricular tracings were recorded. It has occasionally been possible to obtain tracings through the gastric air bubble.

In the thirty subjects, 195 left ventricular tracings were studied (usually four complexes recorded). Of these 98 were taken in the postero-anterior position, 35 with the subject turned five or ten degrees towards the left anterior oblique position with the left ventricular border behind and to the left of the spine, and 62 in the full left anterior oblique. Only a minority of the tracings appeared to resemble the pattern described as typical in the early American publications (Henny *et al* (1947) and Luisada and Fleischner (1949)). This shows a relatively steep upstroke in early diastole, flattening out in late diastole, and followed by a considerably steeper downstroke representing ventricular systole. This downstroke is preceded by a small notch which has been attributed to auricular systole and at the end of the main downstroke a notch is observed coincident with the second heart sound and attributed to closure of the aortic valves.

This idealized ventricular electrokymogram (Fig. 3–5) has recently been criticized by Akman *et al.* (1950) who have pointed out that the time relationship of specific points on the electrokymogram to the corresponding events in the cardiac cycle is approximate only. They have also pointed out that in about half of their cases a rather characteristic pattern is obtained in the oblique position, particularly from the upper half of the left ventricular border. This tracing shows a steep upstroke with a symmetrical convexity followed immediately by a steep downstroke (Fig. 6 and 7).

We have confirmed this finding and in addition have noted that this tracing may be obtained from the half-left and postero-anterior positions although in general the early systolic upstroke becomes more pronounced higher up the left ventricular border and further round to the back. We have recorded it in four instances from the lower half of the left ventricular border in the postero-anterior position (Fig. 7).

Inspection of the tracings has shown that the summit of the ventricular electrokymogram may bear no constant relation to the onset of QRS, either from one subject to another or from one position to another in the same subject. When the summit did not appear to represent the onset of the intrinsic deflection (due to ventricular systole) we have tried such other point on the tracing as seemed more suitable and still found no constant relation to QRS or to the times of aortic and pulmonary artery filling which might represent fairly closely the end of isometric contraction of the ventricles. In Fig. 6 and 7 we believe that the intrinsic deflection representing the onset of the ejection

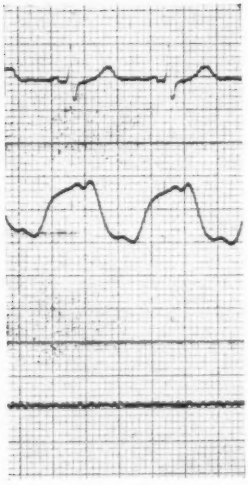


FIG. 3.—Electrokymogram from the lowest position on the left heart border (LV1) in a healthy man, aged 18 years.

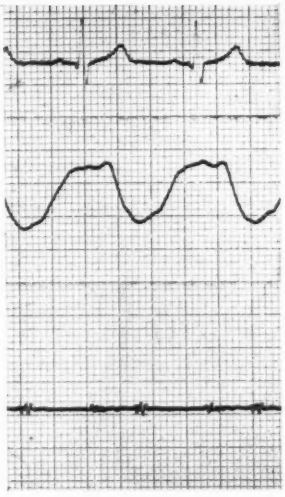


FIG. 4.—Electrokymogram from the LV1 position in a healthy man, aged 27 years.

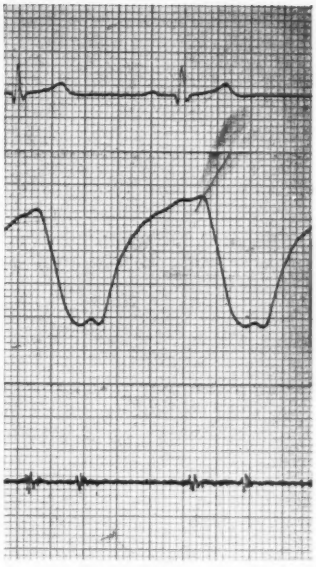


FIG. 5.—Electrokymogram from the LV2 position in a healthy man, aged 22 years.

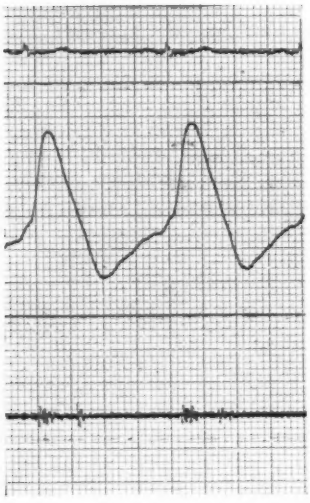


FIG. 6.—Electrokymogram from the lowest (LV1) position in the left anterior oblique in a healthy man, aged 50 years, whose heart was in the extreme vertical position.

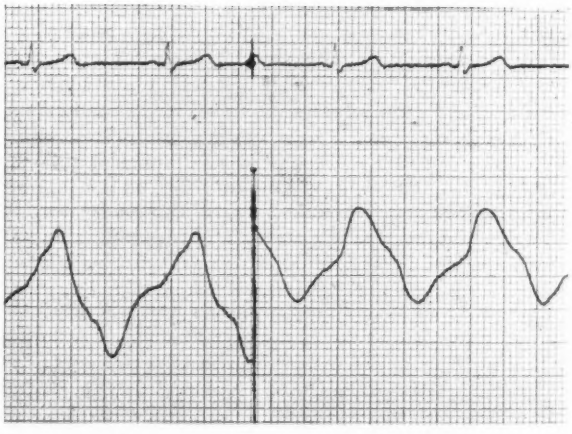


FIG. 7.—Electrokymogram from the LV1 and LV2 positions in a healthy woman, aged 21 years. Note these were obtained with the subject in the postero-anterior position.

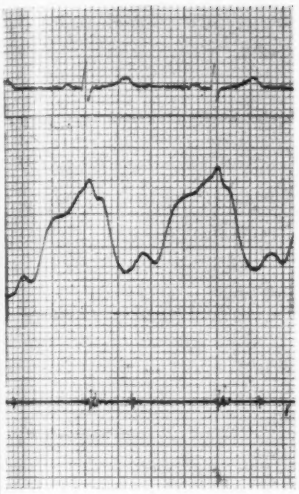
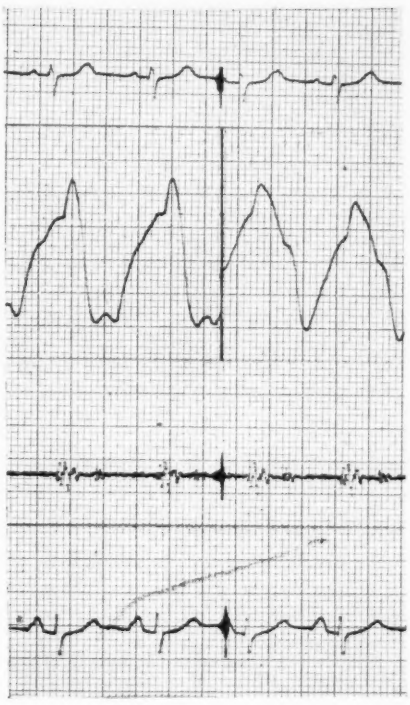


FIG. 8.—Electrokymogram from the lowest (LV1) position in a healthy man, aged 48 years.



LV1 LV2

FIG. 9.—Electrokymograms from the LV1 and LV2 positions in a healthy woman, aged 29 years. Note how in the second tracing, the notch coincident with the second heart sound has now risen to a position half-way up the intrinsic downward deflection.

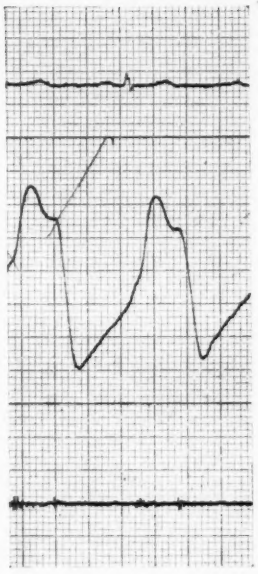


FIG. 10.—Electrokymogram from the LV2 position showing the notch coincident with the second heart sound to be high on the main downstroke.

phase precedes the summit, whereas in another type of tracing (Fig. 8) the onset appears to follow the summit.

Another striking discrepancy is shown by other tracings in which the notch in the electrokymogram, coincident with the second heart sound (Fig. 5 and 8) and accepted by Luisada *et al.* (1948, 1949) as representing closure of the aortic valve, occurred just after the summit and before the main downstroke in one particular position on the ventricular border, although found in its usual position (in the trough) in tracings from other positions (Fig. 9 and 10).

Akman (1950) has criticized the idealistic interpretation of this notch occurring at or near the second heart sound, pointing out that the time relation is only approximate; our finding would suggest that in this instance (Fig. 10) it is not even permissible to attribute the main deflection of the electrokymogram to ventricular systole as the main downward deflection occurs in early diastole. This suggests that the inward movement of the left ventricular border continued after the end of systole and that the main deflection of the electrokymogram in this tracing may be recording the pendulum-like motion of the heart as a whole or some other positional change. Superficial examination might suggest paradoxical pulsation, but there is a normal upward movement in late diastole. In contrast, Fig. 13 shows the electrokymogram from the border of a left ventricular aneurysm in a

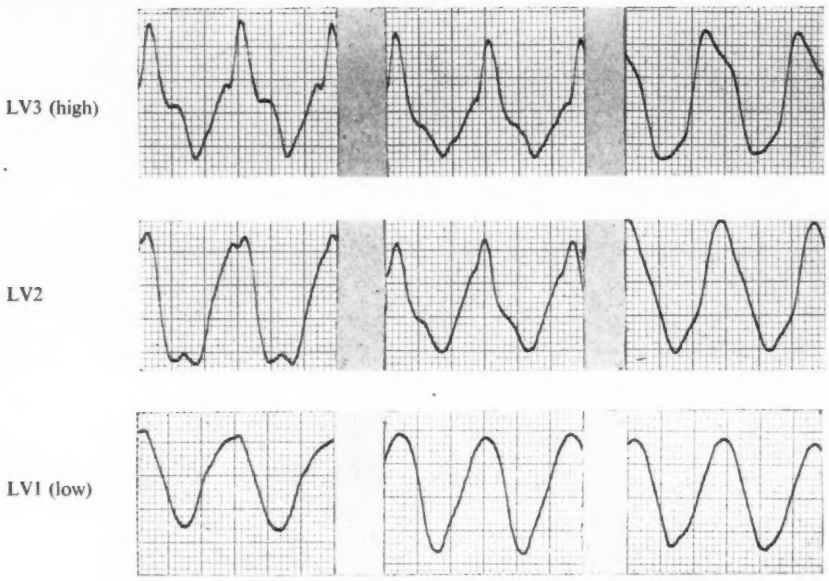


FIG. 11.—These nine tracings were taken from the left ventricular borders of a healthy woman, aged 22 years. Those on the left with the subject in the postero-anterior position, those on the right in the left anterior oblique and those in the middle from an intermediate position. The lowermost tracings were taken from just above the diaphragm, and the others from higher positions on the ventricular border.

patient in whom paradoxical pulsation was noted on screening. In this tracing there is practically no upward movement in late diastole, the paradoxical movement occurring throughout the cardiac cycle.

While it is obvious that the arterial electrokymograms correspond closely with arterial pulse tracings, we cannot agree with the earlier American workers who have tried to attach precise meaning to points on the ventricular electrokymogram on the assumption that it corresponds with a ventricular volume curve. Cardiac movement is highly complex; in addition to systolic contraction and diastolic expansion there is rotation, change in shape, and possibly also pendulum movement. It has been pointed out by Roesler (1943) that the main feature of ventricular systole is considerable shortening of the long axis rather than inward movement of the border. This was demonstrated by Wolferth and Margolies (1939) by roentgenkymography in subjects with calcification of the mitral ring.

In view of the wide variation we have found in the pattern of the normal left ventricular electrokymogram we believe that any future study should include multiple tracings. We feel that a single ventricular electrokymogram is as incomplete as a single lead of the electrocardiogram. Our routine method is to record three tracings from high, intermediate, and low points on the left ventricular border with the subject in each of three positions (postero-anterior, formal left anterior oblique, and an intermediate position with the subject turned five or ten degrees towards the left anterior oblique). Fig 11 and 12 show nine tracings recorded from the same subject in this manner.

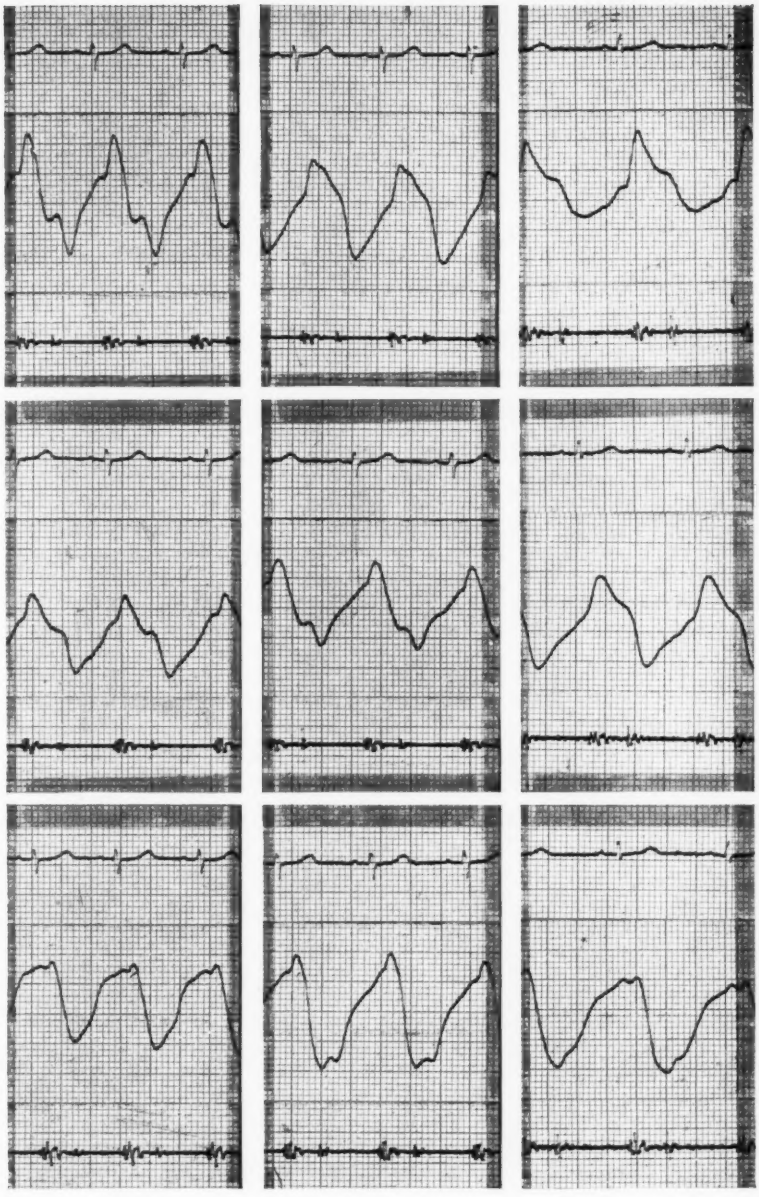


FIG. 12.—Multiple left ventricular tracings from a healthy woman, aged 29 years.

Abnormal Subjects

Twenty-five subjects with abnormal hearts have been studied, the diagnoses have been as follows. Coronary artery disease 6 (one with paradoxical pulsation on fluoroscopy, one with left bundle branch block), hypertension (left ventricular enlargement) 2, Fallot's tetralogy 2, patent ductus arteriosus 2, aortic incompetence 2, atrial septal defect 2, ventricular septal defect 1, aortic stenosis and incompetence 1, aortic stenosis (? bacterial endocarditis) 1, mitral stenosis and aortic incompetence 1, mitral stenosis 1, mitral stenosis with aneurysmal dilatation of the left auricle 1, auricular fibrillation (no other abnormality) 1, anæmia with cardiac enlargement 1, and mediastinal lymphadenopathy 1.

We have only been able to satisfy ourselves that the tracings obtained have been completely outside the normal range in respect of the following observations which have confirmed and amplified findings on cardioscopy rather than added any new information.

In both patients with Fallot's tetralogy we failed to obtain the normal tracing over the region of the pulmonary artery. We have never failed to obtain this tracing in normal subjects or in the other patients listed above.

Tracings from the right heart border in the massive left atrium with mitral stenosis showed complete absence of pulsation even with the sensitivity increased. There was a similar finding over enlarged mediastinal lymph nodes.

In patients with patent ductus arteriosus and atrial septal defect we found large tracings from the pulmonary artery, but we have as yet no measure of the limits of normal. In the patient with paradoxical ventricular pulsation, electrokymography showed a pattern that was interpreted at the time as clearly abnormal (see Fig. 13). Further experience has shown that tracings not unlike this may be obtained from normal subjects (e.g. Fig. 6, 10). In these, however, the tracings show a prolonged gentle upward movement preceding the onset of QRS followed by the sharp upstroke believed to be due to positional change of the heart during the early part of ventricular systole. The tracing from our patient with cardiac aneurysm shows a downward movement in late diastole with very little slow upward movement before the sharp rise at 0·04 sec. after Q. This confirms the impression of other observers who have stressed that the findings in early systole should be interpreted with great care, and that the diagnosis of paradoxical pulsation must depend on abnormalities throughout the cardiac cycle. We have not found such abnormalities in other patients with known previous infarction in whom cardioscopy had revealed no evidence of aneurysm.

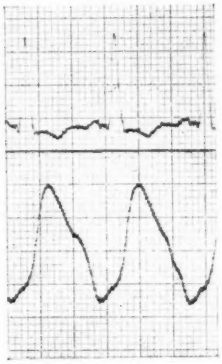


Fig. 13.–Subject, woman, aged 56 years. Screening showed paradoxical pulsation of the upper part of the left ventricular border. The tracing was taken from this region with the subject in the postero-anterior position.

Summary

Observations on electrokymography are presented after experience with fifty normal and twenty-five abnormal subjects using a Sanborn electrokymograph and poly-viso 4-channel recorder.

Analysis has been made of the pulmonary artery and aortic electrokymograms, time relations being studied with simultaneous recording of the electrocardiogram.

Criticism of previously published interpretations of the left ventricular electrokymogram has been made and the wide variation of normal illustrated and stressed. A method of recording electrokymograms from nine positions on the left ventricular border is described and is recommended for the routine study of left ventricular movement.

Preliminary observations on subjects with various cardiac abnormalities have been made.

We wish to thank Dr. William Phillips for his constant encouragement and help, Mr. R. G. Wood (Physicist) for his advice and Miss C. Rumbelow (Cardiographer) for technical assistance.

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THE MOVEMENT OF AORTIC AND PULMONARY VALVES STUDIED POST MORTEM BY COLOUR CINEMATOGRAPHY

BY

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This paper describes a method of studying the action of human pulmonary and aortic valves obtained shortly after death. The aim was to study the action of human heart valves in an artificial system, the flow through which was designed to resemble that in the living heart. In this way it was hoped to obtain information that might apply to human surgical problems.

The need for knowledge of valve action is becoming greater as surgical treatment of pathological aortic and pulmonary valves becomes established. The majority of surgical techniques in this field have been evolved from morbid anatomical studies and experiments on living animals. Recent work by Bailey *et al.* (1950) and Brock (1950) illustrates the difficulties of surgical approach to aortic stenosis.

Particular attention has been paid to the behaviour of normal and abnormal valves with alterations of flow and rate. A preliminary study of the action of stenosed aortic valves before and after division of fused commissures has been made. A similar study has been reported by Smith *et al.* (1950), but their experiments were mainly concerned with photographing valve action in the experimental animal.

Method. Fresh hearts were obtained from the post-mortem room with the ascending aorta cut across about one inch above the aortic valve. Fig. 1 shows the method of setting up the preparation. The ascending aorta was fixed round the perspex tube below the viewing chamber by a ligature at A. A threaded metal tube, B, was tied into the left ventricle in the apical region and passed through a plate, C, into the chamber, D. By screwing the nut, N, the heart was stretched taut between aorta and apex. The nut also made a water-tight joint between D and the space E round the heart which was open to the atmosphere. In this way fluid from D could pass through the pipe into the ventricular cavity, through the aortic valves into the viewing chamber, F, and out to the " peripheral circulation."

Movement of the valves was photographed by a cine-camera placed over the viewing chamber. The peripheral circulation consisted of a vertical tube filled with water, the top of which was open to the atmosphere. A closed air-filled side arm was incorporated in order to simulate the elastic recoil of the aorta. Variations in the height of the column altered the pressure against which the system had to work. The apparatus was perfused with water under constant pressure from an outside source. An electrically operated solenoid valve, G, controlled the flow into chamber D. A similar valve, H, controlled the outflow to the atmosphere.

G and H were controlled by an electronic switch, I. When G was open, H was shut, and vice versa, and so an intermittent flow was obtained. The proportion of inflow to outflow time could be altered, and also the overall rate.

The camera used was an electrically operated cine-camera specially adapted for photographing objects through water at a range of six inches.

* Assisted by a grant from the Endowment Fund of St. Thomas's Hospital.

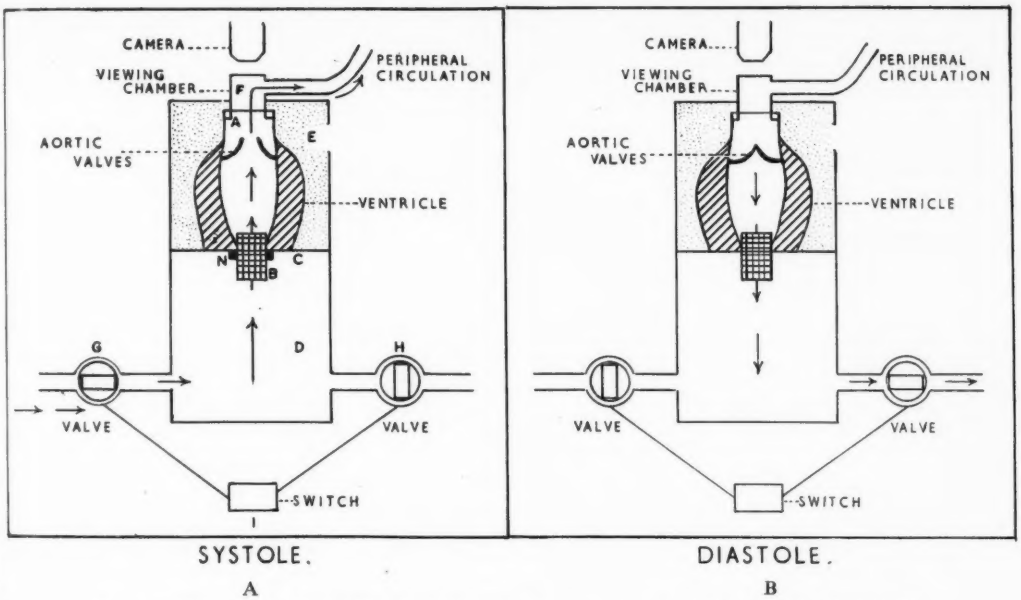

FIG. 1.—Diagram of system with valves arranged to correspond to systole (A) and to diastole (B).

RESULTS

A maximum intermittent flow of three litres through the valves was obtained. The aortic valves closed as soon as the intraventricular pressure fell sufficiently. When normal aortic valves were used pressures distal to the valve of about 120 mm. Hg "systolic" and 80 mm. Hg "diastolic" could be obtained. There was also a prominent dicrotic notch when the valves closed. Pressures in the chamber proximal to the valves were about 120 mm. systolic falling to 0 mm. diastolic. Pressures were recorded with a Sanborn electromanometer. Pressures were not recorded before and after division of commissures in stenosed bicuspid and stenosed aortic valves, but following commissure division the flow through the valves increased in two experiments from 2 to 3 litres a minute in the stenosed aortic valve and from $1\frac{1}{2}$ to $2\frac{1}{2}$ litres a minute in the stenosed bicuspid aortic valve. Cinematograph films have been made of the following conditions (Fig. 2 and 3).

(1) Normal aortic valves. (2) An aortic valve believed to be incompetent in life. (3) A stenosed aortic valve before and after division of the fused commissures. (4) A bicuspid aortic valve before and after division of the fused commissure. (5) A normal pulmonary valve.

DISCUSSION

Aortic and pulmonary valves have a simple mechanical action. In order to approximate as nearly as possible to the conditions under which they behave in man the following factors should be considered.

Flow. Three litres a minute is the maximum so far obtained but it is hoped to increase this considerably and it should be possible eventually to obtain flows approximating to the human cardiac output during moderate exercise.

Pressure distal to the valves. This was controlled by the height of the peripheral column and was readily adjustable. The pressures were arranged to be as near as possible to those in life. It is

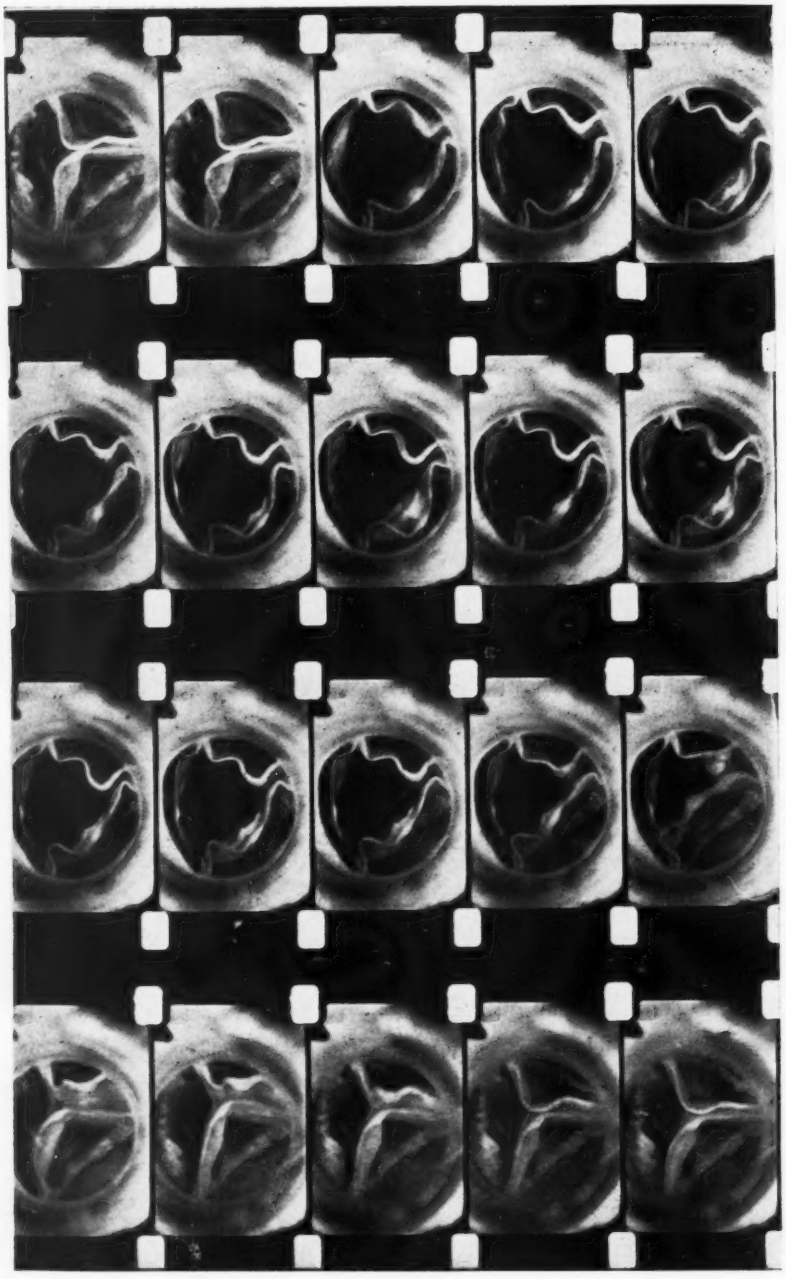

FIG. 2.—Normal aortic valve. Photographs from the film showing a complete cycle of opening and closing.

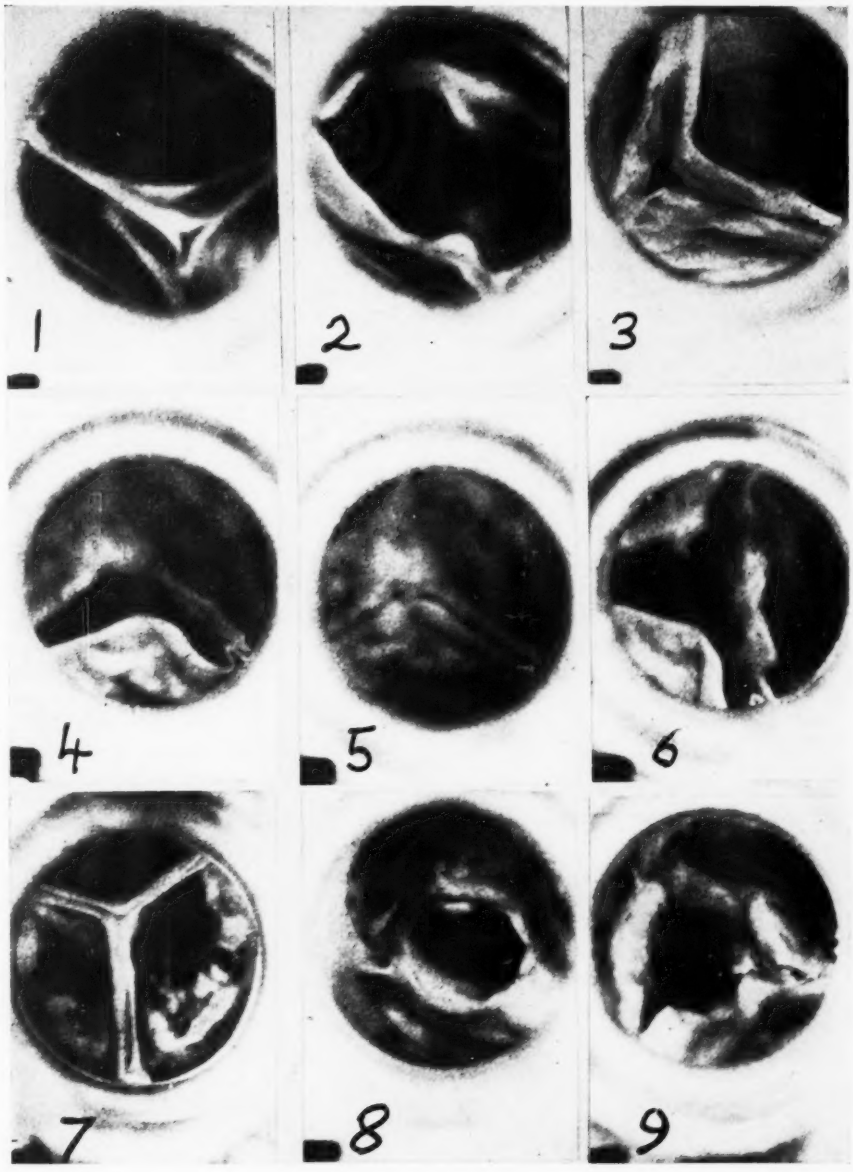

FIG. 3.—(1) Pulmonary valve shut and (2) open. (3) Aortic valve from a patient who had evidence of aortic incompetence in life. (4) Bicuspid aortic valve open, and (5) shut and (6) with commissure divided. (7) Aortic valve with calcified plaques in the cusps. (8) Stenosed aortic valve and (9) the same valve with commissures divided.

technically difficult to reproduce in a model a peripheral resistance that is at all similar to the peripheral resistance of man. We are aware of the present limitations of the apparatus.

Rate. As already described this was controlled by the electronic switch.

Viscosity. This problem has not yet been studied but experiments are proceeding using translucent fluids of viscosity approximating to the viscosity of blood.

It has been possible so far to perfuse a normal heart under the following conditions—a flow of three litres a minute maximum, pressures comparable to normal blood pressures, and rates between 60 and 80 a minute. From this it is apparent that the pressure can be satisfactorily arranged. It is hoped to increase flow and rate and to study the problem of viscosity. By this method, variations in these four factors can be arranged to comply with the known clinical data of the specimen under trial.

Division of two stenosed valves has produced an increase in flow. With this encouragement it is proposed to extend the study of the effects of operations on stenosed valves and the efficiency of plastic operations for repair of incompetent valves. These manœuvres can be carried out with human material, such as pericardial or fascial grafts, or with prostheses. Successful procedures can be further studied on experimental animals as a step in the evolution of human operative treatment.

SUMMARY

A method is described of intermittent perfusion of human hearts post-mortem and of photographing the action of the aortic and pulmonary valves.

Films were made of normal aortic and pulmonary valves and of stenosed, bicuspid, and incompetent aortic valves.

The physiological factors that need to be reproduced are discussed. Suggestions are made for future work.

Our thanks are due to Professor W. G. Barnard, Dr. L. Hewlett and Dr. D. Teare for access to the pathological material. We would like to express our grateful thanks to Dr. Evan Jones for his interest. We would also like to thank Mr. P. Stiles for the design of the switch and to Messrs. B. J. Lynes, A. E. Clarke, F. Thomas, R. W. Halls and A. L. Wooding for technical assistance.

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PULMONARY CAPILLARY ARTERIAL PRESSURE PULSE IN MAN

BY

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In 1948, Hellems, Haynes, Dexter, and Kinney, using venous and arterial catheterization in dogs obtained pressure recordings from both sides of the pulmonary capillary bed. The method consisted in wedging the tip of a cardiac catheter into a small branch of the pulmonary artery and of the pulmonary vein respectively, and recording the mean blood pressures in the obstructed vascular bed distal to the catheter tip. They felt that these pressures were " close approximations of the true capillary pressure " and the term capillary pressure is now widely used for the mean pressure obtainable by occluding a small branch of the pulmonary artery. Shortly afterwards, it was shown by Lagerloef and Werkoe (1949) that in man the tracings recorded on the arterial side of the capillary bed were of typical venous shape and closely resembled the tracings from the right (and left) atrium. They concluded that in the manometric system thus constructed not only capillary pulsations but also those from the venous side of the vascular bed were transmitted through the capillaries.

It seemed, therefore, of interest to investigate the type of curve obtainable by obstructing a small branch of the pulmonary vein. Accordingly this was done in five cases of atrial septal defect, and the tracings thus recorded resembled in many ways arterial pulsations. Since Lagerloef and Werkoe called their curves from the arterial side the " pulmonary capillary *venous* pressure pulse " (PCV) we should like to name the curves from the venous side of the capillary bed the " pulmonary capillary *arterial* pressure pulse " (PCA).

Methods. Cardiac catheterization was performed in the usual way. Cournand catheters No. F6–9 with the hole on the tip were used and connected with Tybjaerg-Hansen's capacitive manometer. Pressure tracings were recorded on Elmquist-triplex, together with electro- and phono-cardiograms. The damping of the manometer system was critical. In order to eliminate artefacts due to catheter movements, damping was further increased by the electrical filter III on the amplifier. The mean pressures were highly overdamped curves using filter V. The zero point for all pressures was 5 cm. below the sternal angle, with the patient in the recumbent position. Immediately after pressure recording blood samples were drawn in the usual way and oxygen analyses were carried out using Van Slyke's method. To obtain pulmonary capillary arterial pressures the catheter was advanced through the right and left atrium and into a pulmonary vein under fluoroscopic control. The patient was then asked to take a deep breath, and the tip of the catheter was pushed further into the vein so as to obstruct its lumen.

OBSERVATIONS

In three of the five cases studied we made a diagnosis of pure atrial septal defect, in one atrial septal defect with complete transposition of the great vessels, and in one atrial and ventricular septal defect with dextrocardia, complete heart block, and probably complete transposition. The diagnosis was based on the results of catheterization, angiocardiography, and clinical findings. Since no case was suitable for surgical treatment the diagnosis could not be verified.

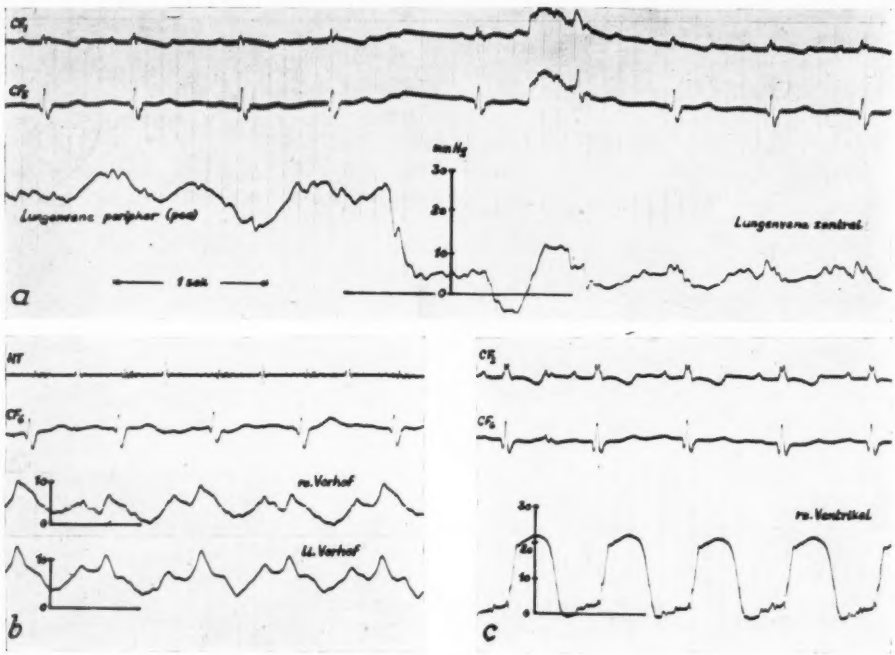

FIG. 1.—Case 1. (A) Withdrawal of the catheter from the occluded branch of a pulmonary vein under continuous pressure recording. (B) Superimposed tracings of the right and left atrial pressures. (C) Right ventricular pressure.

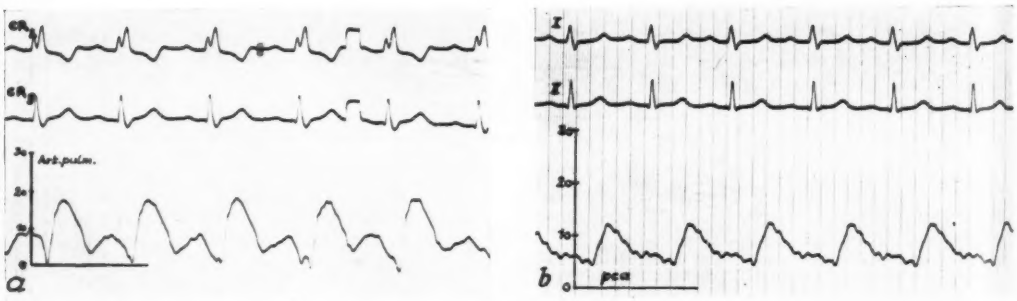

FIG. 2.—Case 3. (A) Pulmonary arterial pressure. (B) Pressure in the obstructed pulmonary vein.

Case 1. A girl, aged 9, with isolated atrial septal defect. The tracings of Fig. 1 were obtained in a right pulmonary vein, the catheter having been passed through the A.S.D. By obstructing a small branch of the vein, a curve resulted in which no venous elements can be recognized, its mean pressure being about 23 mm. Hg. Though disturbed by many artefacts these venous elements due to atrial contraction may be clearly seen after withdrawal of the catheter under continuous pressure recording. Simultaneously with the change in the shape of the curve, there occurs a sudden drop of pressure which is now in the mean about 5 mm. Hg. Pressures in the left and right atria were also recorded, and since the heart rate during both measurements was the same it was possible to superimpose both tracings.

Case 2. A boy, aged 8, with atrial septal defect with complete transposition of the great vessels. Several pulmonary veins were entered. Again an " arterial " pressure pulse of 27/20 mm. Hg was obtained, and again a sudden drop of pressure simultaneously with the appearance of atrial waves was seen upon releasing the catheter tip from the obstructed venule. Attempts to enter the pulmonary artery arising in this case from the left ventricle failed.

Case 3. A woman, aged 20, with isolated atrial septal defect with gross dilatation of the pulmonary artery. An arterial tracing in the blocked pulmonary vein was obtained in this case with a lower systolic and a higher diastolic pressure than in the pulmonary artery (Fig. 2). The onset of the systolic pressure rise was delayed by about 0·1 sec. indicating that this pulsation was transmitted through the capillaries. A typical venous curve in an obstructed pulmonary artery has also been recorded, and its mean pressure was found to be well below the mean pressure in the obstructed pulmonary vein.

Case 4. A man, aged 18, with atrial and ventricular septal defect with dextrocardia, complete heart block, and probably complete transposition. By advancing the catheter through the saphenous vein, a left-sided inferior vena cava, and both atria, several pulmonary veins were entered. The tracings obtained in the right atrium, which received blood from all the pulmonary veins, showed high cannon waves due to simultaneous atrial and ventricular contractions. These and also the normal a-waves are absent in the PCA tracing superimposed in Fig. 3, its mean pressure now being well above the atrial mean pressure. High pressures were recorded in both ventricles, but the pulmonary artery could not be reached.

FIG. 3.—Case 4. Superimposed tracings from the blocked pulmonary vein and from the right atrium which was functionally the left.

Case 5. A boy, aged 16, with atrial septal defect and pulmonary hypertension and cyanosis. High pressures were found in the right ventricle and in the pulmonary artery presumably due to highly increased arteriolar resistance. Unfortunately, no attempts were made to enter the capillary bed from the arterial side. A " hæmodynamic alternans " will be recognized in the right ventricle, in the pulmonary artery, and also in the obstructed pulmonary vein (Fig. 4) thus proving the transmission of arterial pulsations through the capillaries. The time lag of the onset of the systolic pressure rise amounted to 0·07 sec. This was the only case where the mean pressure in the right atrium was higher than in the left. It may, therefore, be assumed that the apparent cyanosis was, at least partly, due to a predominant right to left shunt.

DISCUSSION

As it will be seen from the tracings shown above the pressure pulsations obtained by occluding a small branch of the pulmonary vein (PCA) appear to have the following characteristics. (1) The shape of the curve resembles in many ways an arterial pulsation. (2) The mean pressure is higher in the obstructed than in the non-obstructed pulmonary vein and in both atria. (3) A considerable

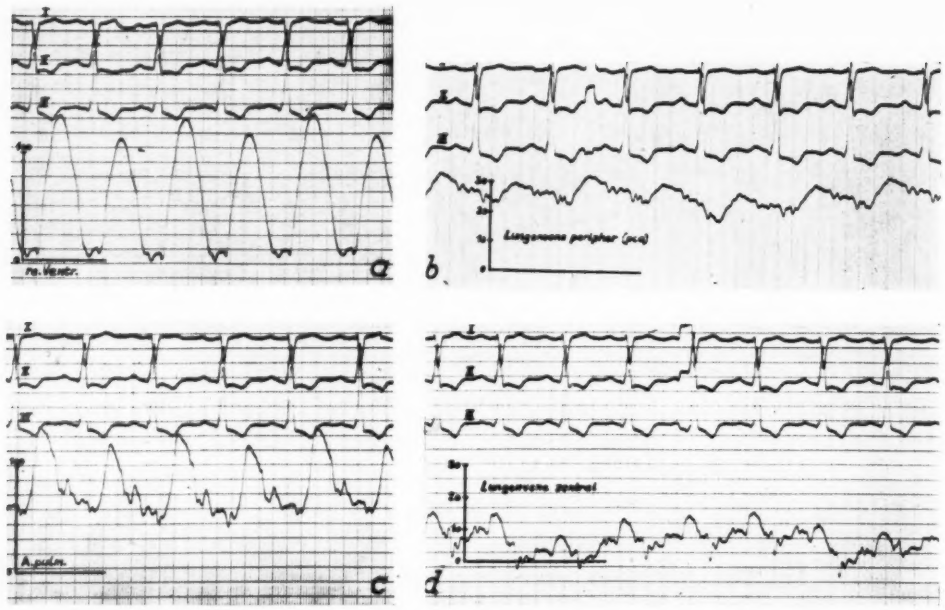

FIG. 4.—Case 5. (A) Right ventricular pressure. (B) Pressure in the obstructed pulmonary vein. (C) Pulmonary arterial pressure. (D) Pressure in the non-obstructed pulmonary vein.

time lag exists between the onset of the systolic pressure rise in the pulmonary artery and in the blocked pulmonary vein.

Further evidence for the PCA being a transmitted arterial pulsation has been brought by the observation that in one case showing high cannon waves in the non-obstructed pulmonary vein these could not be seen after obstructing it, and on the other hand, rhythmic variations of the systolic pressure height in the pulmonary artery due to a " hæmodynamic alternans " of the right ventricle have been recorded on the other side of the vascular bed.

In trying to interpret these results one has to recognize that the method of wedging a cardiac catheter into the capillaries is by no means a physiological one. An artificial manometric system is constructed which includes certain parts of the vascular bed and thus disturbs the normal flow and pressure conditions. Obstructing the blood flow on the venous side will result in a certain degree of congestion in front of the catheter tip. But since the capillary bed of the lung contains such a rich network of vessels that equilibrium should easily be adjusted by means of the neighbouring unobstructed capillaries maintaining undisturbed blood flow, this congestion seems unlikely to contribute much to the pressure height and cannot be the only reason for the arterial pulsations and the sudden pressure rise occurring after blocking only a very small branch of the pulmonary vein. To explain these findings we must assume that not only the capillaries but also the arterioles on the other side of the obstruction take part in the manometric system thus constructed. Then, the explanation offered for the venous pulsations observed after blocking a small branch of the pulmonary artery would be that in this case also the venules are included in the pressure conducting system.

It was recently reported by Calazel *et al.* (1951) that they were not able to obtain venous tracings in the obstructed pulmonary artery in five out of six patients, and thus could not confirm the findings of Lagerloef and Werkoe (1949) who stated that their PCV tracings closely resembled the pattern

of the right atrial curves. Using the same manometric system and the same electrical damping as the Swedish workers, we should like to say that in most cases in which we tried to obtain PCV tracings we found rather distinct venous curves in the blocked pulmonary artery. Therefore, the failure of Calazel *et al.* in getting a " capillary " pulse resembling atrial tracings may well be due to the different recording and damping system they used.

We should like to think that the results reported by Lagerloef and Werkoe (1949) and in this paper, support the view of Cournand (1950) that the term " capillary " pressure commonly used for the mean pressure obtainable by blocking the pulmonary artery, is open to question; it is not only the pressure in the capillary bed but also the pressure in the venules on its other side one records by this method, and it is not only the " capillary " pressure but also the pressure in the arterioles one obtains by blocking the pulmonary vein. Otherwise the pressures thus recorded on both sides would be the same.

Identical mean pressures on both sides of the capillary bed were reported by Hellems, Haynes, and Dexter (1949) in two cases of atrial septal defect but could not be found by Calazel *et al.* who recorded in two similar cases PCA mean pressures that were almost twice as high as the PCV mean pressures. This difference was also found in one of our cases and was certainly of the same order in the other cases as well. Since it is now widely held that the " capillary " pressure gives an indication of the left atrial mean pressure, it should be emphasized that an error in the determination of the " capillary " pressure of only 1 mm. Hg will usually result in an error in the range of 10 up to 25 per cent and this will enter into the various calculations which are now used for the determination of pulmonary pressure gradients, pulmonary arteriolar resistance, and mitral valve area (Dexter *et al.*, 1950; Gorlin and Gorlin, 1951).

If we assume that the PCA tracings are arterial pulsations transmitted through the capillaries there is no doubt that the pulsations from the bronchial artery should considerably contribute to the pressure height in the blocked pulmonary vein. Therefore, we were not surprised to find no relationship between the PCA pressures and the pressures in the pulmonary artery or in the right ventricle, respectively. As it will be seen in the Table, in one case the PCA systolic and mean pressures were even higher than the systolic pressure in the right ventricle but since some time had elapsed between the two measurements during which the pressure in the right ventricle might have fallen, no decisive conclusions could be drawn.

TABLE

DATA OBTAINED IN THE OBSTRUCTED AND NON-OBSTRUCTED PULMONARY VEINS, PULMONARY ARTERIES, AND RIGHT VENTRICLES

Case No.	Pressures in mm. Hg				O_2 Saturations (percentage)	
	PV m.	PCA s. d.	PA s. d.	RV s. d.	PV	PCA
1	5	27 21	—	22 0	74·2	72·8
2	8	27 20	—	37* 7	85·6	85·6
3	2	13 4	18 1	25 0	83·0	—
4	8	17 12	—	125† 4	91·0	87·3
5	6	33 23 (29)†	130 56 (115)†	130 5 (110)‡	87·3	—

* Left ventricle † Both ventricles. ‡ Pulsus alternans.

Since a certain degree of dilatation of the pulmonary capillaries, which would facilitate the transmission of arterial pulsations, seems to be persistent with atrial septal defect, these results obtained in pathological cases cannot be readily applied to normal conditions. Considering further the non-physiological method with which these results were obtained, no claim of significance upon the true hæmodynamic conditions on the arterial side of the pulmonary vascular bed should be made.

There is one further point. As was shown by Dexter *et al.* (1946), fully oxygenated blood can be drawn from the capillary bed after blocking the pulmonary artery. It seemed, therefore, of interest to compare the degree of oxygen saturation in the samples drawn from the obstructed and non-obstructed pulmonary veins (see Table). In only three cases was it possible to obtain blood in the PCA position, and in two of them saturation was found to be slightly lower than in the non-obstructed vein. But before discussing the significance of these findings, we should like to wait till further confirmatory results have been gathered. A certain degree of unsaturation of the pulmonary venous blood was found in all patients but this seems to be quite common with atrial septal defect (Hickam, 1949; Wood, personal communication).

Summary

In five cases of atrial septal defect, pressures on the venous side of the pulmonary capillary bed were recorded after wedging a cardiac catheter into a pulmonary vein so as to obstruct its lumen.

Since the tracing thus obtained closely resembles arterial pulsation it is called the " pulmonary capillary arterial pressure pulse."

It is assumed that these pulsations are transmitted through the capillaries from the arterial side of the pulmonary vascular bed.

In all cases the mean pressures in this position were found to exceed considerably the mean pressures in the non-obstructed pulmonary vein and in both atria.

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CONSTRICTIVE PERICARDITIS

BY

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Some 23 years have passed since the suggestion was first made that the symptoms of constrictive pericarditis might yield to surgical treatment (Volhard and Schmieden, 1928). This interval has ripened judgment on the effects of this therapeutic procedure, and it is now opportune to pass opinion on the value of the operation and on other aspects of the condition, especially its ætiology, distinctive physical signs, and the meaning of certain cardiographic and cardioscopic appearances. These are described in the light of our experience with 30 patients who have undergone surgical treatment.

The series was made up of 26 males and 4 females. The youngest patient was 11 years of age and the oldest 63; there were 6 in the second decade, 7 in the third, 3 in the fourth, 6 in the fifth, 7 in the sixth, and 1 was over sixty years of age.

Ætiology and Pathology

White (1935) and Harrison and White (1942), reporting on the progress of 1500 patients with rheumatic heart disease, found among them no instance of constrictive pericarditis. In one of our patients mitral stenosis was found side by side with constrictive pericarditis (Jackson, 1950). This one example does not justify the view that constrictive pericarditis is a rheumatic condition, and we have regarded the association as fortuitous in this patient. Apart from the rarity of mitral stenosis in constrictive pericarditis—one reported case and one in our series—the relative sex incidence of 26 males and 4 females, opposes the suggestion that the pericardial condition may have a rheumatic origin in that mitral stenosis is much commoner in women. A history of rheumatic fever was obtained in two patients only. Acute pericarditis occurred in five, and in four of them it preceded the development of signs of constriction by only a matter of months; in the fifth the attack of pericarditis happened 23 years before.

We bring evidence from our cases to support the view that constrictive pericarditis is the outcome of a *tuberculous* infection. In four there was active tuberculosis in a close relative and in a fifth, in the family where the patient lodged; in a sixth case the patient's father had a deformed spine from Pott's disease. Involvement of the pleura was common and four gave a history of pleurisy, though in none was it proved bacteriologically to be tuberculous in nature; there was a large effusion on the right side in four cases. Pleural thickening was met with on the right side in seven, on the left in one, and on both sides in six. Evidence of tuberculosis was found in four patients who did not undergo operative treatment and for that reason are not included in this series; in one there was fibrosis of lungs and in another active pulmonary tuberculosis; tuberculous glands were confirmed at biopsy in a third, and in a fourth there was tuberculous infection of the elbow joint. In another three patients, treated surgically and therefore included in this series, there was substantial evidence that tuberculosis had caused the infection: in one dissemination of tuberculosis in the lungs and liver, and in another general dissemination, had taken place after the operation; in a third tubercle bacilli were isolated from the pericardial debris removed at operation.

At operation the heart was found encased in a dense and fibrous pericardium which was often as much as 1·0 cm. thick. Both layers were affected, so that the pericardial space was obliterated and fibrous strands often invaded the myocardium making pericardial stripping difficult in such cases. Areas of calcification were common and occurred in 23 of our 30 cases, and especially in the A-V groove. Localized collections of a creamy-white caseous material were often met with in the deeper layers of the pericardium.

Microscopic examination did not supply the ætiology of the disease in most cases and guinea-pig inoculation with the caseous material did not produce the infection. Fibro-caseous tuberculosis of the pericardium was present in two patients, and two others developed miliary tuberculosis though no direct evidence of the infection was obtained from examination of the pericardium. The dense fibrosis with hyalinization, and the sparsity of cells and small vessels is quite unlike the pericardial thickening of rheumatic heart disease (Armstrong, 1940), and we are in agreement with Andrews *et al.* (1948) that tuberculosis is the actual cause of the disease.

Symptomatology

Breathlessness on exertion proved to be the earliest and commonest complaint and it was present in all but two of our patients; in these two the condition was discovered fortuitously, one on re-enlistment in the army and the other during an illness that proved to be glandular fever. Dyspnœa at rest was met with in five patients all of whom had gross ascites. In none was there pulmonary congestion radiologically. Although breathlessness is such a common symptom, it differs from the dyspnœa of pulmonary congestion in heart failure. The symptom portrays an inability to walk apace, but disappears at the moment of halting unless respiration is embarrassed by a high diaphragm from an abdomen distended by ascites. One patient with his hand held at the umbilicus said, " I am all right from here up and I am all wrong from here down," meaning that he was not breathless, but that he was incapacitated by his ascites and œdema of the ankles. Instead of breathlessness we propose the term, *restricted ambulation*, to describe this common symptom of constrictive pericarditis.

Fulness or swelling of the abdomen was a prominent symptom in two-thirds of the patients; it was often an early complaint, and was caused by a distended liver often combined with a varying amount of ascites. *Œdema of the ankles* had been noticed by the same number of patients, and although it appeared earlier than the abdominal swelling in a few, it was commoner to find it developing some time after the ascites, and it was always less noticeable.

Among *other symptoms* complained of were pain in the left chest (but it was never suggestive of cardiac pain), swelling of the face, tightness of the neck, tiredness, and cough.

Physical Signs

Many of the objective symptoms of constrictive pericarditis are found in patients with heart failure, especially when it involves primarily the right side of the heart, and this accounts for many instances of pericardial disease that continue to go unrecognized. In order to emphasize this similarity and point particularly to the signs that lead to an earlier recognition of the condition, we have arranged them in three divisions, the first to include signs common both to constrictive pericarditis and right heart failure, the second dealing with signs unlike those in heart failure, and the third describing physical signs distinctive of constrictive pericarditis.

Signs Common to Right Heart Failure

Examination of the *pulse* in constrictive pericarditis found it similar to that in failure of the right heart. Thus, it was often noticeably small; in 17 patients the pulse pressure was 30 mm. or less and once it was 15 mm. The highest pulse pressure recorded was 50 mm. so that a large pulse was not once found in 30 patients. Lowering of the pulse pressure during inspiration (paradoxical pulse) was not a common finding and we agree with Paul, Castleman, and White (1948), who met with this in rather less than half their cases, that it is not a helpful sign in diagnosis.

The *blood pressure* was never raised in our cases. In only one was the systolic level higher than 135 mm.; in 23 the systolic pressure was 120 mm. or less and in 11 it was under 100 mm.

In 14 of the 30 patients the pulse was regular and normal sinus rhythm lasted throughout the period of observation undisturbed by the injury caused to the heart muscle by surgical interference. *Auricular fibrillation* was present in 13 patients when they were first examined, and it persisted in each case irrespective of any clinical improvement that followed the operation. Fibrillation was commoner in the older group, so that although it was met with in two before the age of 30, ten patients were over the age of 45 years. In three others auricular fibrillation set in after the operation; in two it was paroxysmal, alternating with paroxysmal tachycardia in one, and preceding established fibrillation in the other. In five of the seven patients with fibrillation examined before digitalis was given, the ventricular rate was relatively slow (70 to 90 a minute) and in five of the six cases already taking digitalis it was slower (50 to 70 a minute). A more rapid ventricular rate (over 120

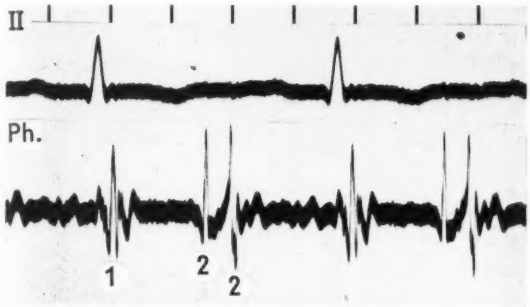

FIG. 1.—Constrictive pericarditis. Phonocardiogram shows splitting of second heart sound. Second or pulmonary component has greater amplitude than first or aortic component. Time interval here and in other figures is 0·2 sec.

FIG. 2.—Constrictive pericarditis. Phonocardiogram showing triple heart rhythm from addition of the third heart sound.

a minute) was met with in four patients, two of them with established and two with paroxysmal fibrillation. In one patient the onset of fibrillation more than two years after the operation had brought no symptoms, and the heart rate was 80 a minute in the absence of digitalis therapy. Conditions that might determine the presence of auricular fibrillation such as cardiac enlargement, heart failure, or excessive pericardial calcification, were looked for, but apart from age, none appeared to favour the onset of the arrhythmia. Extrasystoles, occurring in three patients, were considered to be fortuitous, and no other form of arrhythmia was met with.

When patients with constrictive pericarditis were first selected for surgical treatment, an *adventitious sound* in early diastole was found commonly. At first, clinical auscultation interpreted this as triple heart rhythm from addition of the third heart sound, although it was mentioned at the time in most of them that the gap between the second and subsequent sound was shorter than the one customary for this form of triple rhythm. When phonocardiography was applied to this particular problem it showed that splitting of the second heart sound explained those instances where

the extra sound followed close on the second, while in patients exhibiting the cadence typical of triple rhythm the test confirmed that addition of the third heart sound was the cause. When subsequent clinical examination was fortified by this newer knowledge of the auscultatory findings, differentiation of the two groups no longer gave rise to difficulty. Indeed, it may now be emphasized that, since the phonocardiogram has identified the adventitious sound in both groups, the test need not become routine in the investigation of a patient with constrictive pericarditis, unless there is difficulty in distinguishing the splitting of the second sound from a sound in late systole.

Auscultation in the mitral area and along a line joining this to the xiphisternum, found an adventitious sound in 27 out of 30 cases. In 17 this was found to be a splitting of the second heart sound (Fig. 1) and in 10, addition of the third heart sound had initiated a triple heart rhythm (Fig. 2). Only three times did the two auscultatory signs appear side by side. Triple rhythm was not more likely to be present when physical signs like venous and liver distensions and ascites were prominent or had been present for some time.

A phonocardiogram was recorded in 26 patients and in 18 it was done both before and after the operation. In 22 cases in which splitting of the second heart sound was present in the tracing the interval between the aortic and pulmonary components of the sound varied from 0·04 to 0·10 sec. and the average was 0·07 sec. The interval was a little longer than that which was found in a series of ten healthy subjects all showing splitting of the second sound in the pulmonary area and where an average value of 0·04 sec. was obtained during expiration and 0·06 sec. during inspiration (Leatham and Towers, 1951).

The auscultatory sign in healthy subjects differed in three ways from that heard in patients with constrictive pericarditis; first, the pulmonary component of the second heart sound in the latter group was accentuated and this made it audible some distance from the pulmonary area (where it is heard in health) as far as a line adjoining the mitral auscultatory area to the xiphisternum. Secondly, this accentuated pulmonary sound occurred alongside an easily audible aortic component, and thirdly the interval between the two moieties was sometimes a little prolonged.

In 14 patients where a third heart sound was recorded in the tracing, although it had been audible as triple rhythm in only 10, the interval between the second and third heart sounds varied from 0·10 to 0·22 sec. with an average value of 0·17 sec.; here, too, the interval between the sounds did not differ significantly from the value of 0·19 sec. found in a healthy series (Evans, 1943). It was common for these two auscultatory signs to disappear after a successful operation and we came to recognize the value of this in foretelling favourable progress in individual patients. In the earlier cases where the operative approach had been to the left of the sternum and portions of the rib had been removed so that the heart was in close proximity to the chest piece of the stethoscope, a third heart sound, even though physiological, was easily heard.

An incidental murmur in mid-systole was recorded in three patients, but in a fourth who had mitral stenosis as well, a murmur filled systole and another occupied mid-diastole.

Cyanosis, usually seen in the ears, nose, lips, and fingers, was present in half the cases, and was more conspicuous in those patients in whom the condition was known to have produced symptoms for two or more years. It was absent in the early cases and this should never by itself oppose a diagnosis of constrictive pericarditis.

Distension of the neck veins is a constant physical sign in constrictive pericarditis and it was met with in each of our cases. In 21 where the venous pressure was measured it proved to be under 10 cm. of saline in three, between 10 and 20 cm. in nine, and over 20 cm. in nine. Pulsation of the veins was often observed, but in the majority of patients this was not obvious. Since dyspnœa at rest is uncommon in constrictive pericarditis, the presence of distended neck veins in a patient who is able to lie comfortably in the recumbent posture is a characteristic feature of the disease.

Hepatic enlargement was present in each of the 30 patients, and this physical sign ranks with distended veins as a valuable aid to diagnosis; indeed, if these two signs are missing, the diagnosis of constrictive pericarditis should not be entertained. The degree of liver enlargement depends on the severity and the duration of the illness. In the early cases with mild complaints the liver was

easily felt below the right costal margin, while in those with more prominent symptoms it reached to the level of the umbilicus or lower, and in this event ascites was invariably present. The edge of the liver was always firm or even hard and smooth, and as a rule not tender. In spite of the common incidence of considerable hepatic enlargement, jaundice was never met with.

Ascites was present in 16 cases and in many of these it had been a persistent and troublesome complication up to the time of preparation for operation. It was conspicuous in three of the five patients who have died since the operation and remained or returned in three in whom surgery failed to produce any benefit.

Œdema of the ankles was present in 20 patients, never gross and often slight, even though there was great ascites. Swelling of the face occurred in five patients and in one of these there was no swelling elsewhere.

Signs Dissimilar from those in Right Heart Failure

Pulmonary crepitations were absent on auscultation except in those where the lung showed fibrosis, probably tuberculous in origin. Further, pulmonary congestion was not found on cardioscopy. Absence of such pulmonary signs in a patient thought to have heart failure should turn attention to the diagnosis of pericardial disease.

Evidence of *cardiac enlargement* was never present on clinical examination and the cardiac impulse was usually quiet and often absent; the apex beat when it could be located was never displaced outwards.

Unlike most instances of right heart failure constrictive pericarditis does not give rise to *significant murmurs*. Indeed, should a case exhibit an obvious murmur a diagnosis of the pericardial lesion is unlikely to be the true one. In our series three patients had an immaterial mid-systolic murmur and a fourth showed pan-systolic and mid-diastolic murmurs from associated mitral stenosis.

Another difference between the two clinical states lies in the relative *preponderance of certain signs*. Thus, in constrictive pericarditis ascites may be prominent and œdema of the ankles minimal or absent, while the reverse is true of right heart failure. Again, distension of neck veins and enlargement of the liver are physical signs more prominent in the former condition and at an earlier stage than in the latter.

Distinctive Physical Signs

Although some of the objective physical signs in constrictive pericarditis are common to other conditions, occurring as they do in the absence of orthodox breathlessness, they are distinctive. Nonetheless, when the condition is suspected on clinical grounds confirmation is obtained from electrocardiographic and radiological examination; occasionally liver biopsy is desirable.

The Electrocardiogram

The electrocardiogram is a noteworthy test in any patient suspected of pericardial disease. The tracing is reminiscent of that found in cardiac infarction for the changes in both conditions affect the S–T segment early in the illness, and later they give way to a deformity of the T waves. In constrictive pericarditis, a chronic process, changes in the T wave preponderate although the tracing shows other characteristic faults which will be described first.

It has already been mentioned that *auricular fibrillation* is common in constrictive pericarditis, being present in more than one-third of the cases, and especially occurring in the older patient. The ventricular rate in such patients was not rapid as a rule even in the absence of digitalis therapy. The arrhythmia was not once annulled by the operation. In one instance there was paroxysmal tachycardia, and extrasytoles were found in three cases. The voltage of the curve was seldom low and as a rule it was normal. Exaggerated Q waves were never present. The S–T segment was never abnormal except under the influence of digitalis, but the S wave in lead I was as large as the R wave in 16 of the 30 cases.

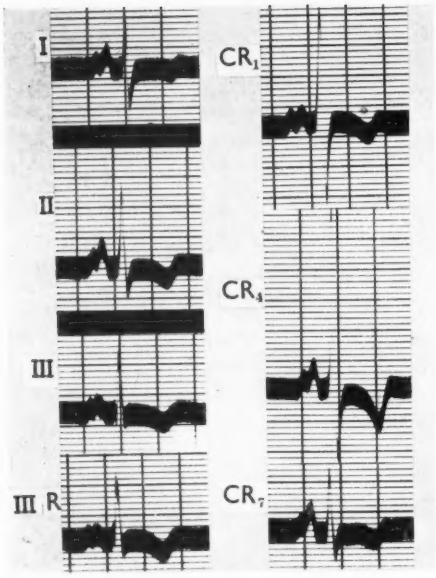

FIG. 3.—Constrictive pericarditis. Notching of P waves noticeable in limb and chest leads. Inversion of T waves in all leads.

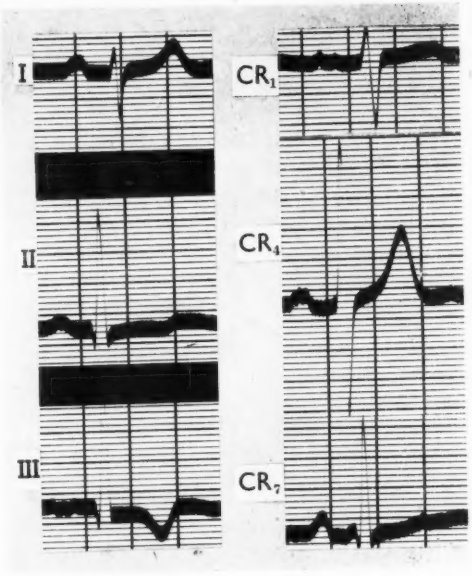

FIG. 4.—Constrictive pericarditis. Inversion of T wave in leads II and III; T very low in CR7. P wave broad and bifid in some leads.

The *P wave* was normal or conventional in only two instances amongst the 17 patients who showed a normal or sinus rhythm. In the remaining 13 cases with auricular fibrillation the P waves had given way to *f* waves which were in no way distinctive. The characteristic deformity of the P wave was a notching and often the first peak was lower than the second so that the wave portrayed a shelf or a step (Evans, 1945). This notching of the P wave might be seen in any or in all limb and chest leads (Fig. 3 and 5). So common has been this cardiographic sign that we have come to regard its presence as supporting the diagnosis of pericardial disease, and proving particularly helpful in those cases where the characteristic T wave inversion does not happen to be a feature of the cardiogram.

The *T wave*, with one exception, was low, flat, or inverted in all the 30 cases; in 11 the T deformity was not gross either in extent or in distribution amongst the leads which included the three chest leads, CR1, CR4, and CR7. The incidence of T wave deformity in the various leads naturally depended on the distribution of the pericardial thickening. Thus, when it was disposed for the greater part postero-laterally the T was inverted in leads II, III, and CR7 (Fig. 4). It was common for inversion of the T wave in CR4 to be added to such changes and sometimes the T was inverted in lead I as well (Fig. 6). While the extent of the pericardial disease was reflected in the number of leads affected, the degree of T wave inversion told of the penetration of the pericardial infection into the myocardium. This was tested as a means of predicting the difficulty met with in stripping the thickened pericardium from the heart; thus, in 10 out of 11 cases in which the changes in the T wave were of a light character the pericardium peeled easily from the heart at operation, compared with the more difficult task in patients who showed deep T wave inversion.

When the post-operative cardiogram was compared with the one recorded before operation it was usually found unchanged and it caused no surprise that sometimes the changes were exaggerated as a result of the damage caused during the pericardial stripping. In eight patients the cardiogram had improved after the operation and the lowered T wave had moved upwards.

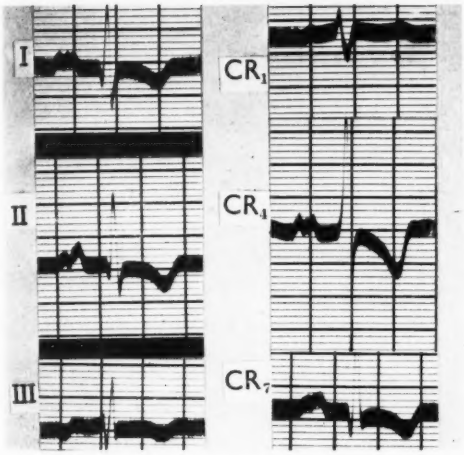

FIG. 5.—Constrictive pericarditis. Inversion of T wave in leads I, II, III, CR4, and CR7. Notching of P waves.

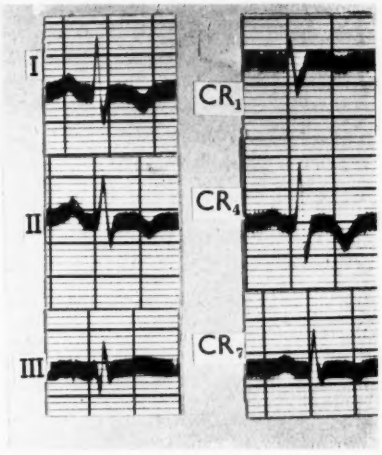

FIG. 6.—Constrictive pericarditis. Inversion of T wave in leads I, II, CR1, CR4, and CR7. P wave notched in lead II.

Radiology

As an ancillary test in the diagnosis of constrictive pericarditis, radiology of the heart is indispensible, and it should always find a place in the investigation of a patient suspected of this condition. It will usually disclose signs that confirm the presence of constrictive pericarditis and these concern pulsation, size and shape of the cardiac silhouette, a characteristic œsophagram, pericardial calcification, and pulmonary changes.

Alteration in *cardiac pulsation* did not help materially in diagnosis, although it was diminished in many. In one patient in whom the constrictive pericarditis involved the waist of the heart, more than ordinary pulsation presented at the border of the left ventricle. Naturally the distribution of the quiet areas varied according to the location of the pericardial thickening, and their importance lies in the diligent search, which such a finding should promote, of the cardiac border for calcification. In a smaller way it may prove useful in guiding the surgeon to the place where stripping of the pericardium will prove most difficult. The radiogram of constrictive pericarditis when the heart pulsation is subdued may show a sharp outline or stencilled appearance of the cardiac silhouette, although the effect is not as noticeable nor as generalized as in the case of pericardial effusion. After a successful operation exaggerated pulsation was seen in the portion of the heart that had herniated through the pericardial opening, and this showed to best advantage in the right oblique position (Fig. 7).

Size and Shape of the Heart. Although constrictive pericarditis does not produce frank enlargement of the heart with obvious hypertrophy of its walls (Parkinson, 1936; Parsons-Smith, 1948) it is common to find an increase of the cardiac silhouette at cardioscopy. Thus, the shadow was greater than normal in 21 of the 30 patients. This apparent enlargement was slight or moderate (Fig. 8) in 17, and it was greater (Fig. 9) in four; in none was it very conspicuous. Whenever the size of the heart shadow was increased, the effect of a raised diaphragm from a greatly distended liver, commonly associated with much ascites, could not be estimated accurately, although it was likely that the distortion it produced was considerable. In four cases examined at necropsy the weight of the heart was slightly in excess of the average normal, and in one pulmonary embolism some eight hours before death had caused much dilatation. The weight of the heart, however,

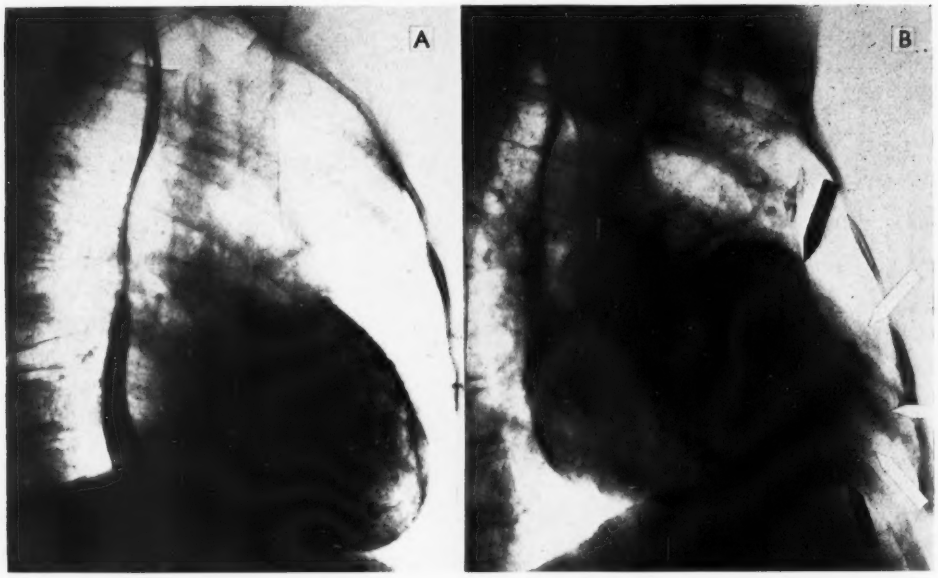

FIG. 7.—Constrictive pericarditis. Teleradiogram R.A.O. (A) Before operation the heart is seen encased by calcium. (B) After operation the heart (white arrows) is seen herniating through opening (black arrows) in calcified pericardium.

was fallacious because it was found impossible to denude the heart wholly of the closely adherent thickened pericardium and this added materially to its true weight.

Whenever constrictive pericarditis had produced much distension of the liver and ascites, the raised diaphragm produced a squat heart shadow with prominence in the region of the left ventricle and more especially of the right side. Even in the absence of this upward displacement, the angle formed by the vascular pedicle and the right auricle was often filled in (Fig. 8 and 10, and Kerley, 1948), causing greater prominence of the right border of the heart. Such prominence was seen in 17 of our patients, while the cardiovascular angle was obscured in 21, in 7 of whom there was no cardiac enlargement. Distension of the superior vena cava was observed in 16 cases.

The Œsophagram. Escape of the left auricle in constrictive pericarditis produces a characteristic picture during a barium swallow in the right oblique position. The left auricular impression in this view is deep (Fig. 11) and closely resembles the change seen in mitral stenosis. In only seven was this radiological effect missing and we have come to regard it as a valuable sign. Although the exaggerated left auricular impression was often somewhat taller than that found in mitral stenosis, this could not by itself decide the diagnosis. The most characteristic distinguishing feature of the œsophagram of constrictive pericarditis was the presence of a relatively clear area between the œsophageal stream and the denser part of the cardiac shadow, whereas in mitral stenosis these two structures usually lay contiguous one with the other. This difference is explained by the displaced *undistended* left auricle in constrictive pericarditis and by the *distended* left auricle in mitral stenosis. Naturally, the diagnosis on this premise gains when the auricular impression is a prominent feature of the case. In one patient this clear area was absent and the dense cardiac shadow reached the barium stream as in mitral stenosis; it became known later that in this instance mitral stenosis was present alongside constrictive pericarditis (Jackson, 1950).

Pericardial Calcification. The presence of calcium in the pericardium, visible on radiological

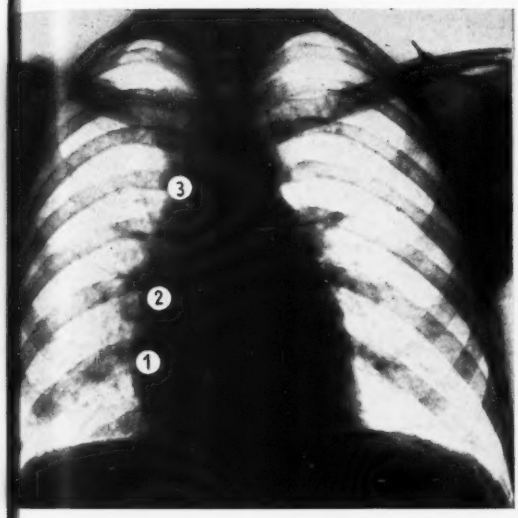

FIG. 8.—Constrictive pericarditis. Slight enlargement of cardiac shadow especially at right auricular border (1). Filling of right cardiovascular angle (2). Prominence of superior vena cava (3).

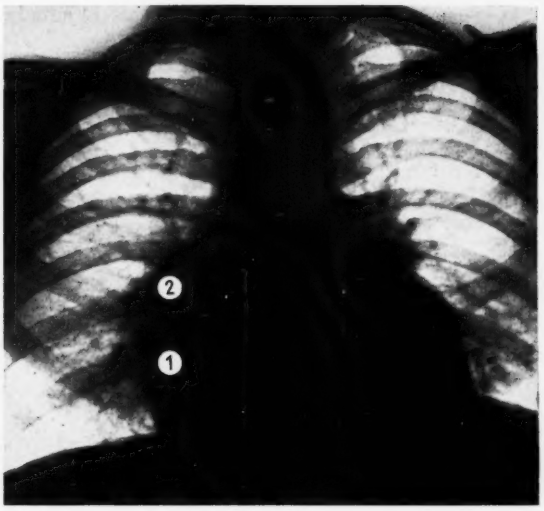

FIG. 9.—Constrictive pericarditis. Considerable enlargement of cardiac shadow where chest is shallow from elevation of diaphragm due to great ascites. Special prominence of right auricle (1), and filling in of right cardiovascular angle (2).

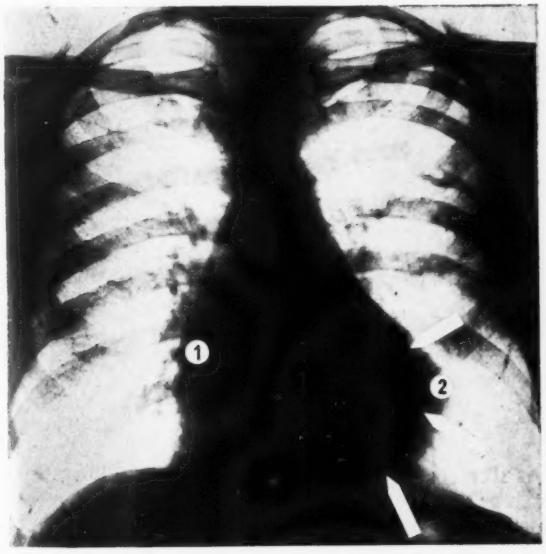

FIG. 10.—Constrictive pericarditis. Filling in of right cardiovascular angle (above 1). Calcium ring (arrows) is within left ventricular border (2) itself displaced to left from escape of heart after operation.

FIG. 11.—Constrictive pericarditis. R.A.O. position. Prominence of left auricular impression (1). Barium stream separated from denser shadow of heart by light zone. Rim of calcium (arrows).

examination, provides valuable evidence of constrictive pericarditis, and for this reason it should be sought diligently during cardioscopy. First, it should be looked for specially in those areas where cardiac pulsation is most subdued, and if missed during cardioscopy it means that the examination has been carried out without searching purposefully for this change. Calcification was present in 21 and absent in 9 of our cases. In 19 the calcium appeared as an incomplete ring, an appearance created by viewing the calcified pericardium end on. During screening in the anterior position a dense strip may be detected first at the left ventricular border (Fig. 12), and in this event attention should be turned next to the inferior border where it is seen like a saucer upon which the heart appears to rest (Fig. 13); the patient should then be examined in the left oblique position where the calcification is usually seen to best advantage appearing as a cup holding the heart (Fig. 14).

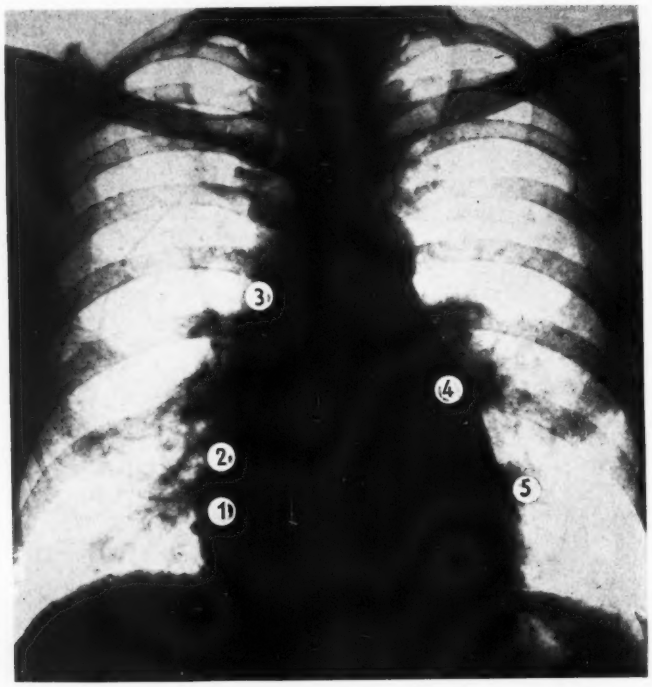

FIG. 12.—Constrictive pericarditis. Slight enlargement of cardiac shadow especially at right auricle (1). Right cardiovascular angle (above 2) filled in. Prominence of superior vena cava (3) and of left cardiac border probably by left auricle (4). There was no mitral valve disease. Strip of calcium (5) at left ventricular border.

Occasionally a completed ring of calcium is seen within the cardiac shadow from calcification in the A-V groove, while in others only scattered or single plaques of calcium are visible.

Changes in the Lungs. In 14 patients the lung fields were clear except for incidental emphysema in one; in the other 16 there were changes in both lungs in 6 and confined to the right in 9 and the left in one. Hydrothorax and pleural thickening, once with calcification, were the common findings, occurring separately or together. The changes suggested the ancillary effects of a tuberculous infection although in cases where the aspirated pleural fluid was examined bacteriologically, the tubercle bacillus could not be found.

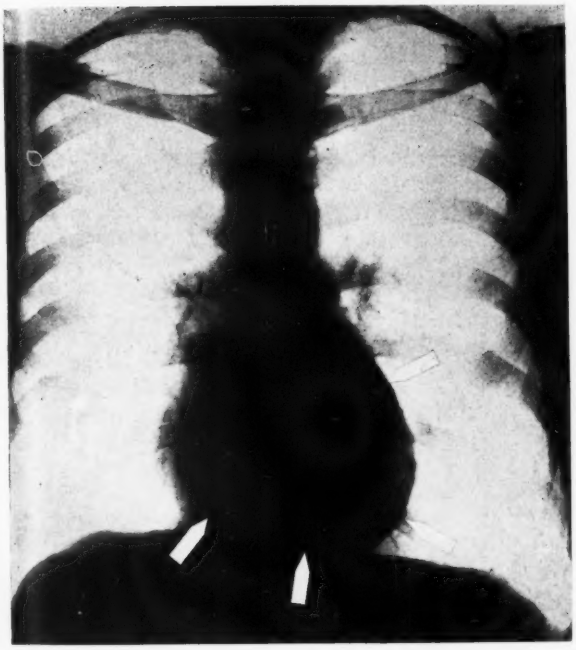

FIG. 13.—Constrictive pericarditis. Heart encased by ring of calcium (arrows) especially prominent at left and inferior borders.

FIG. 14.—Constrictive pericarditis. Left anterior oblique. Heart appears held cup-like by calcified band (arrows).

Liver Biopsy

Among the 4200 necropsies examined by Koletsky and Barnebee (1944) there were 30 with congestive cirrhosis; constrictive pericarditis was the cause of the cirrhosis in 5 cases. They applied a diagnosis of cirrhosis only when there was alteration in the architectural pattern of the liver in addition to fibrosis. The liver from five patients with constrictive pericarditis showed greater fibrosis and distortion of pattern than did any of the others in their series. Increase of connective tissue was specially prominent in the portal zones together with proliferation of bile ducts. In two of three others where the pericardial condition had been present for a shorter period of 4 to 14 months there was also slight cirrhosis. The morphological distinction between well-developed Laennec and congestive cirrhosis is obvious, but in the early stages the differentiation may be difficult. Central fibrosis only occurs in the congestive form, and even when the fibrosis is chiefly portal in its distribution the congestive type usually shows central hyperæmia with atrophy or necrosis of the parenchyma. Moreover, in congestive cirrhosis the nodules of the liver parenchyma are irregular in shape and join up with one another while those of Laennec cirrhosis tend to be circular, circumscribed, and isolated.

The appreciation of the common incidence of hepatic fibrosis in constrictive pericarditis has the greatest value in determining the prognosis of this condition and predicting the progress anticipated from surgical treatment. A liver biopsy was carried out in seven of our cases. In three the specimen retrieved was inadequate and did not allow opinion on the histological pattern; in three there was fibrosis and in one there was much central congestion without fibrosis. Our experience with liver biopsy obtained either by drilling or by puncture has emphasized the difficulty and the uncertainty of the operation and it is unlikely to become a routine procedure on that account.

FIG. 15.—Constrictive pericarditis. Early congestive cirrhosis of liver.

FIG. 16.—Constrictive pericarditis. Severe congestive cirrhosis of liver.

There is hardly need of a liver biopsy in the early cases where the symptoms have lasted less than two years because in these, although hepatic fibrosis is almost invariably present, its severity is not such as to retard recovery after surgical treatment of the pericardium (Fig. 15). In patients where constrictive pericarditis has lasted a longer time a knowledge of the extent of the liver damage is very desirable for it may be so great as to predict failure of the procedure of cardiac decompression as a means of relieving the symptoms, and ascites may persist as the direct outcome of the hepatic fibrosis (Fig. 16).

Progress

Twenty-five of our 30 patients are still alive and have been watched since the operation of cardiac decompression for periods of six months to thirteen years; the average period has been four and a half years.

Five patients are dead, one of them from empyema three weeks after operation. Considering that the condition had sometimes been present for many years and the degree of distension of the liver and ascites, the infrequency of early deaths has been regarded as very satisfactory. Two patients who gained no benefit from the operation died, one after four months and the other after two years: in the latter, abdominal paracentesis had to be carried out monthly as before the operation and she ultimately died suddenly from pulmonary embolism; necropsy showed severe congestive cirrhosis of the liver which itself was considered to be the cause of recurring ascites; there was also miliary tuberculosis of the lungs. The fourth patient derived immediate benefit from the operation, but died after a short illness eight months later from meningitis and generally disseminated miliary tuberculosis. The fifth, aged 59, died ten years after the operation which had enabled him to resume his duties actively as an engineer and rescued him from invalidism and confinement to his house that had lasted for two years.

Six of the 25 living patients gained benefit from the operation, but since they continue to have symptoms and need digitalis and mercurial diuretics to overcome fluid-retention, they are counted here among the unsuccessful cases; one of them, however, has mitral stenosis; another improved for four years before the symptoms returned, and a third, although with a limited exercise tolerance, has returned to work in the Post Office after an enforced absenteeism of nine months and indifferent health for five years. One patient who has returned to his work as a window dresser six months after his operation has not been classified because it was considered premature to assess his ultimate prognosis.

The operation of cardiac decompression has removed the symptoms in the remaining 18 so that it has succeeded in 65 per cent of the patients in our series who have already survived for an average period of five years since operation. These patients follow their customary occupations without complaints and a few statements from them illustrate the great relief obtained from surgical treatment. An electrician, aged 61, states five years after the operation, " I can climb 90 stairs without trouble." A lift attendant, aged 50, states two years after the operation, " I have not felt so well for ten years." A clerk, aged 48, states two years after invalidism involving recurrent hydrothorax, ascites, and œdema, " I have never looked back." An electrician's mate, aged 54, states one year after the operation, " I can do anything." A bricklayer, aged 28, states six years after operation, " I can work double union rates for 10 hours a day." The remaining patients who gained satisfactory benefit from cardiac decompression include a schoolboy, a blacksmith's mate, an officer in the military police, a man who served three years at sea during the war, and a girl who has married and borne one child since her operation 11 years ago. Naturally, certain signs remain in some of them, such as distended neck veins, auricular fibrillation, and an abnormal cardiogram, but by themselves these do not prove a handicap.

The value of surgery in the treatment of constrictive pericarditis has been widely proclaimed and our experience supports this favourable view of a procedure which can frequently change a life of helpless invalidism to one of ease and even of usefulness, and often restores sound health. Improvement in anæsthesia and surgical technique has reduced the immediate risks of the operation in recent times, and a comparison of the results obtained in separate published series suggests that favourable results from surgical treatment show an increase in the past decade from about one among two cases to two among three (Table I).

According to Santy *et al.* (1946) and Mortensen and Warburg (1948) the results are less favourable in older patients and in the presence of calcification, but our experience does not support this view. Thus, the average age of our successful cases at the time of operation was 35 against 31 years for those who did not benefit to the same extent. Similarly, the degree of calcification was the same

TABLE I

A COMPARISON OF THE RESULTS OF CARDIAC DECOMPRESSION IN PATIENTS WITH CONSTRICTIVE PERICARDITIS REPORTED BY DIFFERENT AUTHORS

Author	Number of Cases	Mortality Rate (Percentage)	Successful Results (Percentage)
Sodeman (1941)	Review	33	50
Edwards and Barlow (1946)	20	25	50
Santy, Berard, and Piquet (1946)	—	—	50
Mortensen and Warburg (1948)	20	45	35
Sellors (1948)	21	19	66
Paul, Castleman, and White (1948)	42	25 (excluding 6 deaths from other disease)	60
Evans and Jackson (1951)	30	13	65

in each group. In our experience there is one overriding factor that influences the success or otherwise of the surgical treatment of constrictive pericarditis, and it is the extent to which congestive cirrhosis of the liver has already taken place. It is a common event among even the early cases, but when the effects of constrictive pericarditis have been present for some years the liver injury is so great that even when its cause is removed it will by itself prevent recovery from symptoms, especially ascites. Such knowledge should impel us to diagnose constrictive pericarditis early and to apply surgical treatment before the liver damage has reached an irrecoverable stage.

Preparation for Operation. Cardiac decompression for the relief of symptoms caused by constrictive pericarditis should not be undertaken as an emergency operation and need never be done in a hurry. When the diagnosis has been substantiated there remains the decision to be taken on treatment, and for this purpose the patients belong to one of three groups.

In the *first* group are those patients who have recently suffered from acute tuberculous pericarditis, usually with pericardial effusion early in the illness, and where the clinical and cardiographic signs of constrictive pericarditis have appeared. A decision has to be taken on the most favourable time to resort to surgery. The period of waiting need not be long, and we think that the operation should take place as soon

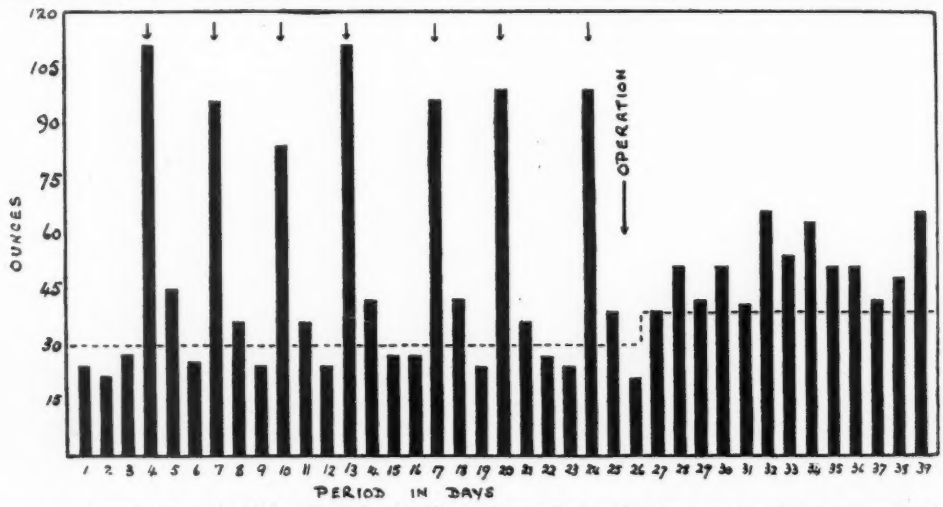

FIG. 17.—Constrictive pericarditis. Fluid intake (discontinuous line) and urinary output (black columns) shown before and after operation of cardiac decompression. Arrows indicate intravenous injections of 2 ml. of neptal.

as it has been shown that the urinary output is never equal to the measured fluid intake, and that the use of mercurial diuretics is needed to prevent fluid retention, this usually showing as ascites (Fig. 17). We favour operating early in such cases and think that surgical treatment should take place even when the symptoms are objective in kind in the belief that subjective symptoms are inevitable later and that their absence need not delay the operation.

Belonging to the *second* group are those cases showing evidence of tuberculosis in places other than the pericardium. A decision on surgical treatment in such cases is always difficult, but it should never be precipitate and adequate time should be devoted to conservative treatment. If tuberculosis shows in a joint like a knee or elbow, as adenopathy in the neck, as fibrosis or cavitation or miliary nodules in the lungs, in addition to the pericardial lesion, a state of partial hæmatogenous dissemination may be presumed to have taken place, and months should be allowed to elapse before releasing the heart by piece-meal removal of the thick pericardium that encases it. Indeed, the wisdom of waiting may find proof in the rapid extension of tuberculosis and the demise of the patient during this period of observation. Such instances are uncommon, but we have met with three.

The *third* group includes patients in whom the condition has been present for some time, often for two or more years. In these cases a liver biopsy is helpful; should it show conspicuous congestive cirrhosis, surgery is unlikely to bring benefit, for the ascites is likely to persist after relief of the pericardial condition. Should liver biopsy prove favourable and a decision be made to operate the patient should be rested in hospital for four weeks on fluid and salt restriction, with digitalis, and weekly injections of a mercurial diuretic; if ascites is a prominant sign it should be dealt with initially by paracentesis. The aim is to bring the patient to the operating table free from pleural effusion, ascites, and œdema. In these instances especially, a quiet persistence in sound medical treatment should never yield to the impatience that is inseperable from the anticipation of the more spectacular results of surgery.

Summary and Conclusions

Our experience with 30 cases of constrictive pericarditis that received surgical treatment has allowed us to draw the following conclusions.

The condition is caused by tuberculosis, and generally the infection is confined to the pericardium apart from an innocuous involvement of the pleura; its presence elsewhere should delay surgical interference.

Constrictive pericarditis, characterized by great thickness, often with caseous changes at its centre and frequently showing calcification, differs from the flimsy adherent pericardium that is a common and incidental finding at necropsy.

Although breathlessness on exertion is common it does not tally altogether with the dyspnœa of heart failure in that halting gives instant relief and there is never pulmonary congestion; we have thought it should be designated differently and suggest for it the term restricted ambulation. When the diaphragm is raised significantly through the presence of great ascites, respiration becomes embarrassed even at rest.

Two-thirds of the patients complained of fulness or swelling of the abdomen and as many of swelling of the ankles. The pulse was usually small, and the blood pressure, which was not once raised, was often low. Auricular fibrillation was present in more than one-third of the cases, when the ventricular rate proved to be relatively slow even in the absence of digitalis.

An adventitious heart sound was heard along a line joining the mitral area to the xiphisternum in 27 out of 30 patients; in 17 it came from splitting of the second heart sound, and in 10 it was in the form of triple rhythm from the addition of the third heart sound. A diligent search for these auscultatory signs is essential for an examination that tests the presence of constrictive pericarditis, because their absence almost excludes the diagnosis. Disappearance of the signs after a successful operation was common and itself predicted a favourable outlook.

Cyanosis was not found early in the illness, but full neck veins were always present; so also was distension of the liver: if these two signs are absent the diagnosis of constrictive pericarditis should not be entertained.

Absence of crepitations over the lung bases, of pulmonary congestion at cardioscopy, of much cardiac enlargement, and of significant heart murmurs, in the presence of preponderant ascites over œdema, are signs that help to distinguish constrictive pericarditis from failure of the right heart due to any cause including valvular disease.

The electrocardiogram often showed auricular fibrillation, but its particular characteristic was a deformity of the T wave, and also of the P wave in those without fibrillation. Thus, the form of the P wave was altered in all save two cases, and this consisted of notching where the second peak was usually taller than the first, producing a step or shelf; this change supported the cardiographic diagnosis of constrictive pericarditis in the less common cases where characteristic deformity of the T wave was inconspicuous. A low, flat, or inverted T wave was present in all patients with one exception; in 19 the changes were very noticeable, and in 10 out of 11 where the T wave deformity was less noticeable, the work of peeling the pericardium from the heart proved a relatively easy task compared with the laborious stripping in those with deep inversion of the T wave, for in these the pericardial inflammatory process penetrated into the myocardium. The distribution of T wave changes depended on the area affected by the pericardial condition. Thus, the T was inverted in leads II, III, and CR7, or in these and in CR4, while sometimes inversion of T wave in lead I was added to such changes. Exaggerated Q waves were never seen so that a significant Q accompanying a deformed T wave should be identified with myocardial rather than pericardial disease.

Radiology of the heart proved an indispensible corroborative test in the diagnosis of the pericardial condition, and some or all of the following changes were found in our 30 cases: slight or moderate enlargement of the cardiac silhouette, prominence of the right border, filling of the cardiovascular angle on the right side, calcification, absence of pulmonary congestion, and prominence of the left auricular impression in the right oblique with barium in the œsophagus; this last change differed from that met with in mitral stenosis in that between the barium stream and the heart shadow there was a relatively clear area. Calcification of the pericardium was present in two-thirds of our cases; this sign, so valuable in diagnosis, need never evade careful cardioscopy if it is sought in three special places: in the anterior view it is seen end-on as a strip along the left ventricular border and/or mesially below the heart which it appears to support saucer-like; in the left anterior oblique view the calcium line shows even to better advantage and may be likened to an eggcup holding the heart.

The common incidence of congestive cirrhosis in constrictive pericarditis lends importance to an examination by liver biopsy, but the procedure is difficult and the uncertainty of gaining sufficient material opposes its routine use. It is of value, however, in long-standing cases with great hepatic enlargement and ascites, because it should help in such cases to decide whether the hepatic fibrosis is severe enough to maintain ascites even when the pericardial effect is removed at operation.

Treatment by cardiac decompression where the heart, particularly both ventricles, was denuded of the thick pericardium brought relief to most of our patients and especially when the condition was dealt with early and before cirrhosis had so developed as to produce its own effects. For this reason, an earlier recognition of constrictive pericarditis should be our constant aim, for in the absence of surgical treatment it progresses tardily but inexorably towards hopeless invalidism and beyond the aid of any form of therapy.

The operation of cardiac decompression in our earlier cases was carried out by the late Mr. A. Tudor Edwards, and in our more recent cases by Mr. Vernon Thompson who has generously placed his notes of the cases at our disposal. Three patients were under the care of Sir John Parkinson, one under Professor Clifford Wilson, one under Dr. Lloyd Rusby, and another under Dr. R. R. Bomford. The material removed at operation, and at necropsy in five instances, was examined by either Professor Hubert M. Turnbull, Professor D. Russell, Dr. W. W. Woods, or Dr. J. R. Gilmour, at the Bernhard Baron Institute of Pathology.

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RHEUMATIC FEVER IN YOUNG ADULTS

BY

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During and immediately following World War II the opportunity presented itself to observe numerous cases of rheumatic fever in young adults. The present study was undertaken from patients admitted to the Brooke General Hospital over a period of one year. There were four hundred patients admitted for rheumatic fever during this time. Observation of each patient included the history, physical examination with special attention to the heart, complete blood count, examination of urine and stools, sedimentation rate, electrocardiogram, X-ray, and fluoroscopic examination. The diagnosis was based on these findings. Only if at least one major manifestation such as polyarthritis, carditis, chorea, old history of rheumatic fever, or nodules was present with several of the minor ones, such as fever, rash, epistaxis, leucocytosis, elevated sedimentation rate, and anæmia was the diagnosis made. Two hundred and two of these patients, all enlisted personnel of the Army, were diagnosed as having rheumatic fever, and were followed for several months, the average stay in the hospital being six months. Many have been observed for one year or more before discharge.

Clinical Features

Age of Patients. The patients' ages ranged from 17–39 years; the largest groups were 18 years with 65, and 19 years with 63 patients. Between the ages of 17–20 there were 166 (82%); between the ages of 21–29 there were 29 (14%) and from the ages of 30–39 there were 7 (3%).

Number of attacks before and after enlistment. There were 40 patients (20%) who gave a previous history of definite rheumatic fever. This compares with 24 per cent of the group reported by Quinn (1947). Both these figures are smaller than that of 36 per cent found by Manchester (1946) in his study of rheumatic fever in naval personnel. One hundred and sixty-two patients had their initial attack after enlistment.

Family history. Twenty-four (12%) of the 202 patients gave a positive family history of rheumatic fever

Month of onset. The greatest number of cases occurred during the months of January, February, March, and April. As shown by other investigators, rheumatic fever may occur at any time of the year but is most frequent in the spring and autumn months.

Prodromal disorders. There were 137 patients (77%) who had a preceding upper respiratory infection. The diagnoses in order of frequency were: catarrhal fever, tonsillitis, pharyngitis, laryngitis, and bronchitis. The term " catarrhal fever " implied a non-specific febrile illness of the upper respiratory tract. Many of the patients had throat cultures that showed a hæmolytic streptococcus. There were 19 patients who had scarlet fever before their rheumatic fever and 2 who had fever of undetermined origin. Forty patients gave no history of any preceding infection. There were four instances of unusual infections including acute parotitis, acute mastoiditis, pneumonia, and appendicitis. The interval between the prodromal infections and onset of rheu-

matic fever was up to 10 days in 91, between two and four weeks in 61, and four to ten weeks in only 10 patients.

Thus the number of patients who gave a history of no preceding infection is higher than the 10 per cent found by Quinn (1947), but approximates to the 19 per cent of Manchester (1946).

Type of onset. One hundred and seventy-three patients (86%) gave a history of acute polyarthritis. There were 12 patients whose onset was one of general constitutional illness with fever, malaise, muscular aching, and anorexia. Four patients had chest pain as the initial symptom, while 10 gave low back pain as their initial symptom. Two patients complained of abdominal pain and in one, an eighteen-year-old boy, the onset was with acute chorea.

Incidence of fever, leucocytosis, and sedimentation rate. Fever was present on admission in 181 patients (89%). Leucocytosis was present in 118 patients (58%). A raised sedimentation rate was the most consistent positive laboratory finding on admission. One hundred and ninety-four patients (96%) had elevation of the sedimentation rate whereas only eight (4%) did not. Of these eight, four gave a previous history of rheumatic fever; two followed scarlet fever; one followed a hæmolytic streptococcal throat infection; and one had acute pericarditis. Five of these patients showed no permanent cardiac involvement.

The sedimentation rate thus proved to be the most consistent laboratory test and also was valuable in following the progress of the disease in each patient. Nevertheless it is clear that rheumatic fever and rheumatic heart disease can occur without any elevation of the sedimentation rate. The height of the sedimentation rate showed no relation to the severity of the disease, but the duration of elevation seemed to have some significance. In 123 patients who had a raised sedimentation rate for less than eight weeks, 53 developed carditis; in 55 who showed a raised sedimentation rate for longer than eight weeks 42 were found to have cardiac lesions.

Response to salicylates and weight fluctuation. The response to salicylates was recorded as good in 151 (74%) patients; in 29 (14%) it was fair, and in 9 there was no response. Thirteen did not receive salicylates. Eighty-seven (43%) patients lost weight during their illness; in some instances this was as much as fifty pounds.

Initial joints involved. In 173 (86%) patients joint pain was the initial symptom. There were only 26 instances in which non-weight bearing joints were involved. One hundred and thirty-five patients incriminated the weight bearing joint with one of the upper extremities. In 12, the initial joint involved was not clear.

Some of the unusual instances of initial joint involvement included two cases of a painful, swollen, tender temporo-mandibular joint and seven patients who complained of a swollen, painful great toe. There were ten patients in whom initial joint pain followed trauma to that particular joint. Glazebrook and Thomson (1941*a*) noted eleven cases in their series in which the first joint affected was the site of the recent trauma.

Development and Incidence of Murmurs

Each patient was examined frequently in various positions and in both phases of respiration by a member of the staff. Twenty-four patients had significant murmurs on admission. There were 178 patients who had no murmur on admission. Ninety-five (53%) of these suffered significant cardiac damage from this attack. Eighty-three patients (47%) showed no evidence of residual cardiac damage.

The percentage incidence of these murmurs is shown in Table I. There were seven cases of a presystolic apical murmur (Table II). This murmur was described as low-pitched, rumbling, less often blowing, heard in late diastole, often crescendo in character and associated with a systolic murmur. The average duration of the time from admission to when the murmur was first heard in these seven cases was 149 days. Glazebrook and Thomson (1941*b*) discussed the changing heart murmurs in acute rheumatism and noted the early appearance of a presystolic murmur in some cases. In three of their patients it developed within four, six, and nine weeks of the onset of the

TABLE I

DEVELOPMENT OF MURMURS IN 202 PATIENTS WITH RHEUMATIC FEVER

		%
Apical systolic	48	27
Aortic systolic	3	2
Aortic and apical systolic	7	4
Aortic and pulmonary systolic	2	1
Apical and pulmonary systolic	13	7
Mitral presystolic	7	4
Aortic diastolic	15	8
	95	53
Pulmonary " functional " murmurs	21	12

TABLE II

DEVELOPMENT AND INCIDENCE OF APICAL PRESYSTOLIC MURMURS

Case	Age	Previous Attacks	Murmurs on admission	Time after admission PS heard (days)	Duration of raised ESR (weeks)
1	19	none	none	150	40
2	20	none	none	75	36
3	19	1	AS	240	7
4	17	none	AS	180	16
5	18	none	AS	157	36
6	18	none	AS	92	6
7	18	none	AS	150	15
			Average	149·1	22·1

PS=presystolic. AS=apical systolic. ESR=sedimentation rate.

disease. The earliest onset in the present group was 75 days. In the seven cases, there were four who showed cardiac enlargement.

The relation between the clinical appearance of the presystolic murmur and anatomical mitral stenosis is not certain. It is doubtful whether anatomical stenosis could develop in such a short time. In 1935, Bland *et al.* studied the necropsy findings and clinical records of 100 patients who had rheumatic fever. They felt that " after the first year and often becoming more extensive during subsequent years the structural alterations of the mitral leaflets assume increasing importance. Although considerable deformity may develop during the second year, scarring of sufficient extent to produce stenosis at the mitral orifice is rarely present before the third year." In their total series mitral stenosis was considered to be present in 68 instances. In these 68 cases with mitral diastolic murmurs only 21, less than one-third, actually had anatomical stenosis of the mitral orifice.

There were 15 instances of aortic diastolic murmurs (Table III). The average time from admission to when the murmur was first observed was 66 days. There were 7 patients in whom this time was 38 days or less. In these 15 patients there were 3 with demonstrable cardiac enlargement by X-ray and fluoroscopy. Two of these gave a previous history of rheumatic fever.

Three patients developed both aortic diastolic and mitral presystolic murmurs while under observation. In one, the aortic diastolic was first observed in 90 days and the mitral presystolic in 180 days. In the second, the appearance of the murmurs was in 37 and 157 days respectively. In the third, the time intervals were 37 and 150 days respectively.

One interesting observation that was made was the development of the so-called pulmonary " functional " murmur; this was observed in 21 patients. A murmur was not present in any of the patients of this group upon admission. It consisted of a grade II blowing systolic murmur heard at the pulmonic area and which changed with respiration or position but did not completely disappear. The exact significance of this development is not clear. It may mean that in these

TABLE III

DEVELOPMENT AND INCIDENCE OF AORTIC INSUFFICIENCY IN 15 PATIENTS WITH RHEUMATIC FEVER

Case	Age	Previous Attacks	Murmurs on admission	Time after admission ADM heard (days)	Duration of raised ESR (weeks)
1	20	1	none	60	9
2	17	none	ASM	90	16
3	17	none	none	150	6
4	19	none	none	55	16
5	19	none	none	152	4
6	24	none	none	28	24
7	18	none	ASM	37	36
8	19	none	none	38	8
9	19	1	none	60	4
10	19	none	none	21	15
11	19	none	none	28	24
12	29	none	none	60	4
13	18	1	ASM	150	44
14	18	none	ASM	37	15
15	19	2	none	26	24
			Average ..	66	17

ADM=aortic diastolic. ASM=apical systolic. ESR=sedimentation rate.

particular cases some form of pulmonary valve or pulmonary artery involvement actually existed. Collection of lymphocytes, Aschoff bodies, œdema and disruption of the elastica have been described by Paul (1927) as occurring in the pulmonary artery.

OTHER SIGNS ASSOCIATED WITH RHEUMATIC FEVER

Spontaneous epistaxis occurred during the initial few days of the acute rheumatic attacks in 21 (10%) of the group.

Rheumatic pneumonitis. In 3 patients there were chest X-ray findings which pointed to this condition. These findings were present during the acute initial stage when the patient had fever and polyarthritis. Physical findings over the chest were usually absent. Whether these were cases of rheumatic pneumonia as described by Epstein and Greenspan (1941) could not be proven.

Subcutaneous nodules appeared in 7 patients and in four instances were quite extensive, appearing over the occipital scalp, cervical and thoracic vertebræ, elbows, wrists, knees, and ankles. Subcutaneous nodules appear in about 20 per cent of cases in both rheumatic fever and rheumatoid arthritis but their pathology has proven to be different (Fingerman and Andrus, 1943).

Four patients showed the typical erythema marginatum which is associated with rheumatic fever.

Pericarditis. There were eight patients who had signs of fibrinous pericarditis in the series. Three of these had a friction rub heard during the first week of illness. None of these three had chest pain and only one had electrocardiographic changes. The other five had no pericardial friction but had changes in the electrocardiogram which consisted of initial elevation of the S–T segments in the limb leads followed by inversion of the T waves in the limb and chest leads. Only one of these 5 patients had chest pain. Two of these had features of special interest. One who was admitted in February did not develop these cardiographic changes until five months later when his clinical picture showed no abnormalities and the sedimentation rate and other laboratory findings were normal. Another, admitted in May, was about to be discharged in November when a final routine cardiogram showed changes which progressed as in the first case. The patient felt well and all laboratory data were normal. No friction rub was heard and the chest

roentgenogram was normal. The T wave inversions persisted until March, five months later, when they became stable and remained inverted.

There were two cases of pericarditis with effusion. Both had electrocardiographic changes but only one had chest pain.

Electrocardiographic Abnormalities

All of the patients had serial tracings taken. These showed significant changes in 124 cases (Table IV). Prolongation of the P–R interval with normal sinus rhythm was the most frequent abnormality, occurring in 64 patients. In a study made by Engleman (1947) of patients admitted to an Army Service Force rheumatic fever centre, 50 per cent showed abnormalities of the electrocardiogram as compared with 61 per cent in the present series. The most common were heart block and significant T wave deformities in leads I, II, and IV.

Partial auriculoventricular heart block with Wenckebach phenomenon and dropped beats occurred seven times but was never an isolated finding.

TABLE IV

Electrocardiographic Changes observed among 202 Cases of Rheumatic Fever

		%
Changes observed in 124 cases		61
T wave abnormalities	30	24
S–T segment changes	13	11
Pericarditis	8	6
Ventricular premature beats	4	3
Arrhythmias (auricular flutter, auricular tachycardia)	6	5
First degree A-V block	64	52
Second degree A-V block	7	6
Complete A-V block	1	1
Intraventricular branch system block (right)	3	2
Complete A-V dissociation	2	2
P wave abnormalities	4	3
QRS abnormalities	2	2
Sinus bradycardia	13	11

There were thirteen instances of sinus bradycardia. The rate ranged from 42–58 a minute during the acute onset of the disease eventually returning to normal. Glazebrook and Thomson (1941*c*) found that bradycardia was a frequent occurrence in the acute attack in adolescents and young men. This bradycardia was considered to have some prognostic significance as half the patients showing it developed permanent cardiac damage compared with only 30 per cent of those without it. In the present group seven of the thirteen exhibited residual cardiac damage.

No correlation was found to exist between the severity of the clinical picture and the electrocardiographic findings.

The relationship of rheumatic fever to rheumatoid arthritis has been discussed by other investigators (Baggenstross and Rosenberg, 1941; Bayles, 1943; Fingerman and Andrus, 1943; Young and Schwedel, 1944). In the present group there were several patients who came from the same areas at the same time and whose clinical course was that of rheumatoid arthritis. One patient whose case is described below showed manifestations of both diseases.

A man, aged 19 years, developed a sore throat and subsequently swollen and painful interphalangeal joints of the second and third fingers of his left hand. When he was admitted on March 10, three weeks after the onset of illness walking was difficult because of pain in his legs. Physical examination showed the heart not to be enlarged. Grade II apical and pulmonary systolic murmurs were present. The left knee was red, warm, swollen, and painful. The electrocardiogram showed a prolongation of the P–R interval. An aortic diastolic murmur was heard for the first time approximately 37 days after admission. All of the proximal interphalangeal joints of the fingers became swollen and quite tender and there was slight swelling and tenderness of both elbows. There was

no leucocytosis. A mild anæmia was present with 3,800,000 red cells and 11·5 g. of hæmoglobin (Sahli). Urine was normal. The sedimentation rate (Westergreen) was 38 mm. in one hour. The electrocardiogram was normal on May 13.

During his stay in hospital the patient's temperature remained normal. On June 12 he developed large subcutaneous nodules over the occipital region, the cervical and dorsal vertebræ, elbows and wrists. In September a presystolic apical murmur appeared. The weekly sedimentation rates remained elevated. A chest X-ray was normal. Films of the hands showed moderate decalcification of the bones in the fingers and wrists. The patient's proximal interphalangeal joints showed fusiform swellings, and were moderately tender.

Discussion

It is not within the scope of this paper to present a complete epidemiological study of this group of patients or the epidemiology of rheumatic fever in the American Army as a whole. Quinn (1947) stated that " the highest rate in the Navy is found in the recruit training centres and service schools. The duty status of the patients revealed nothing of epidemiological importance." Manchester (1946) observed four major factors involved in the occurrence of rheumatic fever in service personnel: (1) infection of the respiratory tract due to the hæmolytic streptococcus; (2) length of service; (3) seasonal influences ; and (4) antecedent rheumatic fever. In the present study all factors played an important role.

It is interesting to compare some of the findings of McCue and Galvin (1948). In their study of 225 patients with rheumatic fever the average age of onset was 7·9 years. A family history was obtained in 17 per cent compared to12 per cent in ours. Fifty per cent gave a history of a preceding upper respiratory infection compared to 68 per cent in the present group. Joint pains were the most frequent complaint in 157 of their patients. In their group 48 per cent showed residual cardiac damage compared to 53 per cent of our patients in their initial attack. There were no deaths in our group during the initial attack.

The two patients who developed abnormal electrocardiograms resembling those of pericarditis were of special interest. Both were clinically normal and were about to be discharged from the hospital. Neither was observed to have a friction rub. This phase of the disease might have been due to a pure delayed " hypersensitivity " phenomenon. It is suggested that all cases of rheumatic fever should have frequent electrocardiograms.

As a new decade in medicine starts with drugs such as adrenocorticotrophic hormone (ACTH) and cortisone, many physicians may lose sight of the fact that rheumatic fever is still almost a pure clinical diagnosis. We have no specific diagnostic test. Physicians in daily practice must rely on their own clinical acuity without which—and without appreciation of the natural history of the disease—no proper evaluation of treatment can be made. It is hoped that clinical studies such as this can provide some measure of help both in diagnosis and treatment.

Summary

A clinical study of 202 enlisted personnel of the American Army with rheumatic fever between the ages of 17 and 39 is presented.

There were 40 patients with a history of rheumatic fever prior to enlistment and 162 with their first attack after enlistment.

A history of preceding upper respiratory infection was given in 137 patients. Nineteen had preceding scarlet fever. Forty gave no history of a preceding infection.

The sedimentation rate was elevated in 194 patients. This was the most consistent laboratory finding and constituted a valuable guide in following the course of the illness. There appeared to be some relationship between the duration of elevation and development of cardiac consequences.

Ninety-five patients (53%) developed murmurs while under observation, in 7 of whom the murmur was mitral presystolic. The average duration from admission to the time the murmur was

first heard was 149 days. There were 15 cases of aortic diastolic murmurs. These developed during observations after an average interval of 66 days. Pulmonary "functional" murmurs appeared in 21 patients.

There were eight instances of fibrinous pericarditis, two with effusion. Of the eight, three had pericardial friction but no chest pain. Two showed no electrocardiographic changes. Two patients were observed to develop electrocardiographic abnormality typical of pericarditis five months after their initial attack. Both showed normal laboratory findings.

Electrocardiographic changes were observed in 124 cases (61%). Prolongation of the P–R interval with normal sinus rhythm was the most frequent abnormality.

One patient developed simultaneously signs and symptoms of both rheumatoid arthritis and rheumatic heart disease.

The diagnosis of rheumatic fever and rheumatic heart disease still belongs in the realm of the clinician. It is a disease which can be easily overlooked when all the criteria for diagnosis are not present and may exist in the active phase even with no elevation of temperature or sedimentation rate. About one half of any group can be expected to develop permanent cardiac damage.

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DIHYDROGENATED ALKALOIDS OF ERGOT IN THE INVESTIGATION AND TREATMENT OF DIASTOLIC HYPERTENSION

BY

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The treatment of essential diastolic hypertension by surgical sympathectomy has given benefit to properly selected patients (Keith *et al.*, 1949). It is reasonable to suppose that adrenergic blockading agents may also be beneficial in the treatment of hypertension, producing a " chemical " sympathectomy.

The fact that crude extracts of ergot produce sympatholytic activity as well as being direct stimulators of smooth muscle was recognized by Dale (1906). He pointed out that administration of such extracts brought about a subsequent paralysis of motor elements having sympathetic innervation and normally stimulated by adrenaline, while inhibitive elements in the same structures were unaffected. Subsequent chemical purification of the crude drug resulted in the isolation of several alkaloids including ergotamine (Stoll, 1920), ergokryptine, ergocornine, and ergocristine (Stoll and Hofmann, 1943). By hydrogenating the reducible double bond of the lysergic acid component of these parent alkaloids, a new series of compounds was produced, namely dihydroergotamine, dihydroergokryptine, dihydroergocornine (Stoll and Hofmann, 1943), and dihydroergocristine.

The actions of these reduced alkaloids differ somewhat from those of the parent alkaloids. Firstly, the adrenergic blocking potency of the reduced alkaloid is always greater than that of the parent compound (Nickerson, 1949). *In vitro* tests on guinea-pig seminal vesicle and rabbit uterus suggest that dihydroergotamine is the least potent and dihydroergokryptine the most potent in this respect. This adrenergic blocking action is probably next in potency to that produced by the B-halo-alkylamines (Nickerson, 1949).

Secondly, the dihydro compounds are less active in the direct stimulation of smooth muscle. They not only fail to stimulate rabbit or guinea-pig uterus *in vitro* (Rothlin, 1947; Rothlin and Cerletti, 1949), but also tend to diminish uterine contraction and to inhibit the stimulant effects of ergotamine and ergometrine on the uterus. Similarly, hydrogenation reduces but does not eliminate the vaso-constrictor actions of the ergot alkaloids (Cerletti and Kallenberger, 1948).

Thirdly, toxicity is reduced by hydrogenation.

The action of these substances on the central nervous system is a mixture of stimulation and depression, but data are limited concerning the dihydro alkaloids.

The extent of adrenergic blockade produced by the dihydro alkaloids in man remains to be thoroughly investigated, and it is important that changes should not be ascribed to these actions which are really due to central vasomotor depression.

Subjects differ in their clinical response to the various dihydro alkaloids mentioned (von Kappert *et al.*, 1949), and in an attempt to minimize these individual variations a mixture of equal parts of

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dihydroergocornine, dihydroergocristine, and dihydroergokryptine was introduced under the name of hydergine (Sandoz).

It was decided by way of preliminary observation to investigate the effect of intravenous injection of a suitable test dose of hydergine in subjects with diastolic hypertension and also to observe the effect of combined oral and intramuscular therapy. Oral therapy alone with dihydroergocornine produced no significant change in blood pressure in the ten cases reported by Bello *et al.* (1950), but these authors observed some fall in pressure following intravenous administration of this alkaloid, as did Bluntschli and Goetz (1947).

The Intravenous Test

Materials and Methods. Fifty consecutive patients, each of whom had diastolic hypertension and were under observation, received the intravenous test. Of these patients 3 had malignant hypertension and 47 had benign hypertension. Of the former, 2 were women and 1 a man, and of the latter, 31 were women and 16 men. Thirty-three of the benign cases had essential hypertension; 7 had had toxæmia of pregnancy, and 7 had a history suggestive of renal disease. Two of the malignant cases fell into the essential category and the other had suffered from acute pyelonephritis on at least two occasions. The ages ranged from 18 years to 65 years. Forty-one of the patients were in bed in hospital at the time of the test and the remaining 9, who had previously been investigated in hospital, returned as out-patients for the test. No form of treatment was carried out at the time of the test, save that phenobarbitone, ½ grain t.i.d., had been given in all cases for more than four days before the test; there is no reason to suppose that this should in any way vitiate the results obtained.

Technique. The test was carried out as follows: the subject was put at rest in bed behind screens in the ward at a quiet time, or, in the case of out-patients, in a quiet room. The blood pressure was estimated at two-minute intervals over a period of 20–40 minutes for in-patients, and one hour for out-patients, so that a base line level was reached under conditions as near to basal as were reasonably possible. An injection of 0·3 mg. of hydergine (containing 0·1 mg. of each of the three alkaloids) was then given intravenously diluted in 5 ml. of normal saline. In 10 patients, it was given over a period of two minutes, as generally recommended. In 10 patients, it was given over a period of one minute, and in 30 patients it was given over a period of 30 seconds. The blood pressure was then taken every two minutes for the first ten minutes, and then every five minutes for the next fifty minutes, following which it was estimated at half-hourly periods.

Results. In all patients the blood pressure was lowered following injection. In every case, the fall in blood pressure commenced within ten minutes of completion of the injection. The figures quoted for the average fall in each group were estimated from the maximum fall which occurred in the subjects mentioned: in each case this fall occurred within one hour, generally within 10–30 minutes.

Patients with benign hypertension fell into two groups in relation to the amount of fall in pressure: (*a*) those with good renal function and minimal arteriosclerosis (41 cases) in whom the average resting pressure was 189/113 mm., and the average fall was 36 mm. systolic and 20 mm. diastolic (Fig. 1A); (*b*) those with poor renal function and/or marked arteriosclerosis (6 cases) in whom the average resting pressure was 232/126 mm. and the average fall 20 mm. systolic and 11 mm. diastolic (Fig. 1B).

The three cases with malignant hypertension all had good renal function and no arteriosclerotic change of significance; the pressure falls were from 246/144 to 196/112 mm. in one; from 258/142 to 202/108 mm. in another, and from 232/152 to 182/124 mm. in the third (Fig. 2).

The depression of blood pressure lasted over a variable period of up to 1½ hours. The systolic pressure fell in direct proportion to the diastolic pressure, but there was no significant statistical

relation between the initial resting diastolic pressure and the amount of fall of diastolic pressure. The comparison with the response of the blood pressure to the sodium amytal test showed that on the whole lability of the pressure as indicated by this latter test was also indicated by hydergine, although it was impossible to foresee which would cause a greater fall in pressure in any given subject. The injection time was not related to the rapidity of fall in pressure.

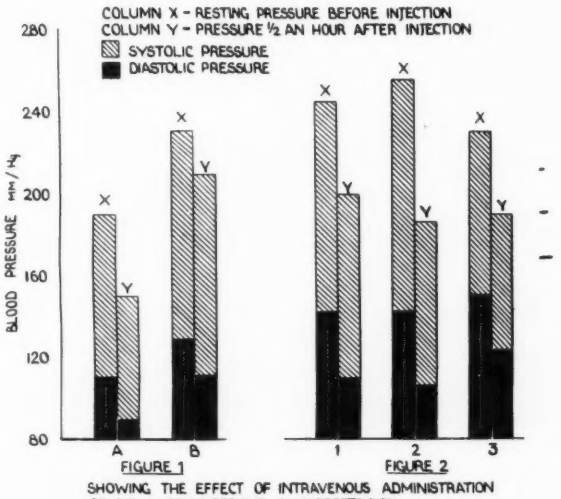

FIGURE 1 FIGURE 2

SHOWING THE EFFECT OF INTRAVENOUS ADMINISTRATION OF 0.3 MG.M OF HYDERGINE IN HYPERTENSION

FIG. 1A AVERAGE FALL OF B.P IN BENIGN HYPERTENSIVES (41 CASES) WITH MINIMAL ARTERIOSCLEROSIS AND GOOD RENAL FUNCTION

FIG. 1B AVERAGE FALL IN B.P IN BENIGN HYPERTENSIVES (6 CASES) WITH ARTERIOSCLEROSIS AND/OR POOR RENAL FUNCTION

FIG. 2 FALL OF B.P IN 3 INDIVIDUAL CASES OF MALIGNANT HYPERTENSION

Before each test, a drop of homatropine was put in one eye of the subject, and observation made of the state of the retinal arterioles, particularly of the amount of spasm present. In 11 subjects, including the three malignant cases, there was marked spasm before injection, and in every one of these the arterioles were observed to " open out " within ten minutes of completion of injection. This effect lasted up to 12 hours in nine cases, and was still present after 24 hours in two.

In all subjects, including the three malignant cases, the cold pressor test was carried out before and half an hour after injection of hydergine. The response to cold in the form of a rise in pressure, both systolic and diastolic, was diminished following the injection of hydergine.

The average rise in pressure in the group of benign cases, with good renal function and minimal arteriosclerosis, following application of the cold stimulus was 42 mm. systolic and 28 mm. diastolic, and half an hour after hydergine was injected the average rise was 14 mm. systolic and 10 mm. diastolic (Fig. 3). In the second group, those with poor renal function and/or arteriosclerosis, the average rise before injection was 22 mm. systolic and 16 mm. diastolic, and after injection was 15 mm. systolic and 9 mm. diastolic (Fig. 4). In the three malignant cases, the rise in pressure averaged 48/32 mm. before, and 17/10 mm., after injection (Fig. 5.)

The only side-effect noted was nasal congestion in 11 cases, lasting for hal fto one hour.

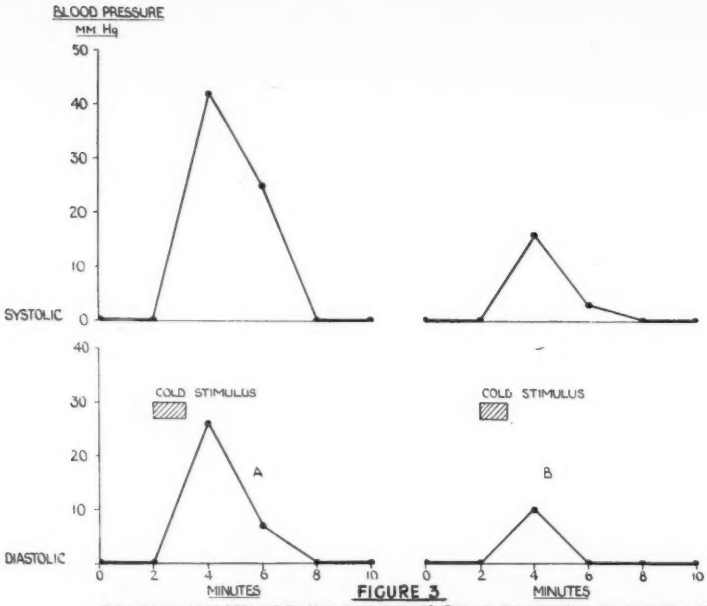

FIGURE 3

THE EFFECT OF HYDERGINE ON THE COLD PRESSOR TEST IN BENIGN CASES OF HYPERTENSION WITH MINIMAL ARTERIOSCLEROSIS AND GOOD RENAL FUNCTION (AVERAGE RESPONSE 41 CASES)

A COLD PRESSOR RESPONSE BEFORE HYDERGINE

B COLD PRESSOR RESPONSE ½ AN HOUR AFTER ADMINISTRATION OF 0·3 MGM HYDERGINE BY INTRAVENOUS INJECTION

TREATMENT

Seventeen patients were selected for treatment, and the effects thereof were observed over a period of at least six months in 12 cases, four months in 4 cases and three months in the other. Sixteen of these subjects had benign hypertension and of these 8 had essential hypertension, 4 had had toxæmia of pregnancy and 4 had a history suggestive of renal disease; the other case had malignant essential hypertension. The only factor excluding a patient from a therapeutic trial was the occurrence of either left ventricular heart failure or congestive heart failure before or at admission. Each patient on admission to hospital had a careful history taken, with particular reference to obstetric and renal factors. For the first week in hospital, a series of investigations was carried out, including the intravenous hydergine test, the urea range test, retinal examination estimation of heart size, a full set of unipolar electrocardiographic leads, and in each case F 933 (piperidyl-methyl-benzodioxane) was administered by intravenous injection to exclude possible pheochromocytoma. Blood pressure was estimated daily with the same sphygmomanometer at the same hour every morning by the same investigator. Readings were taken on each occasion over a period of 15–30 minutes until a constant base line was obtained.

For the first 10 to 14 days, the patients were treated by rest in bed and phenobarbitone ½ grain t.i.d. was the only drug administered. They were allowed up for toilet purposes and for one to three hours in the evenings.

During the third week, an inert preparation of the same taste, smell, appearance, and dispensed from the same bottles as the active preparation, was administered by mouth in the same dosage used for the active preparation. This inert preparation for oral dosage consisted of nux vomica

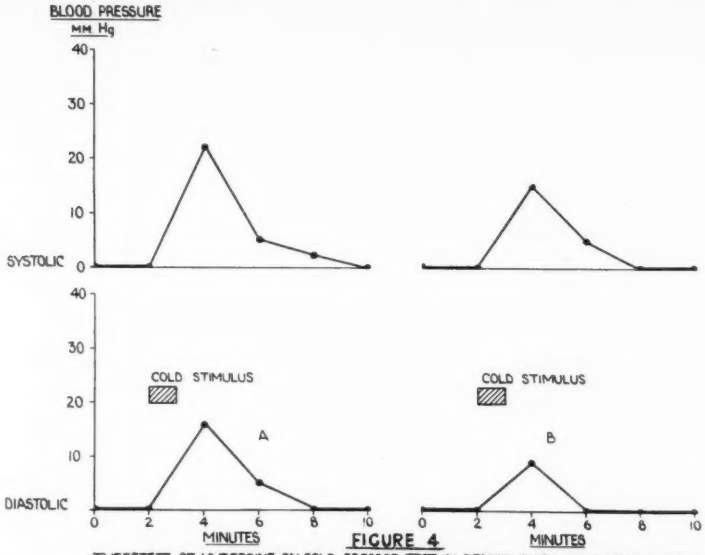

FIGURE 4

THE EFFECT OF HYDERGINE ON COLD PRESSOR TEST IN BENIGN CASES OF HYPERTENSION WITH ARTERIOSCLEROSIS AND/OR POOR RENAL FUNCTION. (AVERAGE RESPONSE FOR 6 CASES)

A COLD PRESSOR RESPONSE BEFORE HYDERGINE

B COLD PRESSOR RESPONSE ½ HOUR AFTER ADMINISTRATION OF 0·3 MGM HYDERGINE BY INTRAVENOUS INJECTION

10 minims, glycerine 1 drachm, water to 2 oz.; 1 ml. of normal saline was given by intramuscular injection daily. In no case did patients know that an inert substance was being given, and all realized that the treatment was being undertaken to investigate its value on their illness.

At the end of this week, three days were allowed to elapse and then hydergine was started by mouth and intramuscular injections for a period of fourteen days in the following dosage:

Day	*Oral dose* minims t.i.d.	*Intramuscular dose* ml.
1	5	0·5
2	8	0·5
3	11	1·0
4	14	1·0
5	17	1·0
6	20	1·0
7	23	1·0
8	25	1·0
9	25	1·0
10	25	1·0

Thereafter 35 minims orally t.i.d.

1 minim of oral solution contains 0·0195 mg. of each alkaloid. 1 ml. of parenteral solution contains 0·1 mg. of each alkaloid.

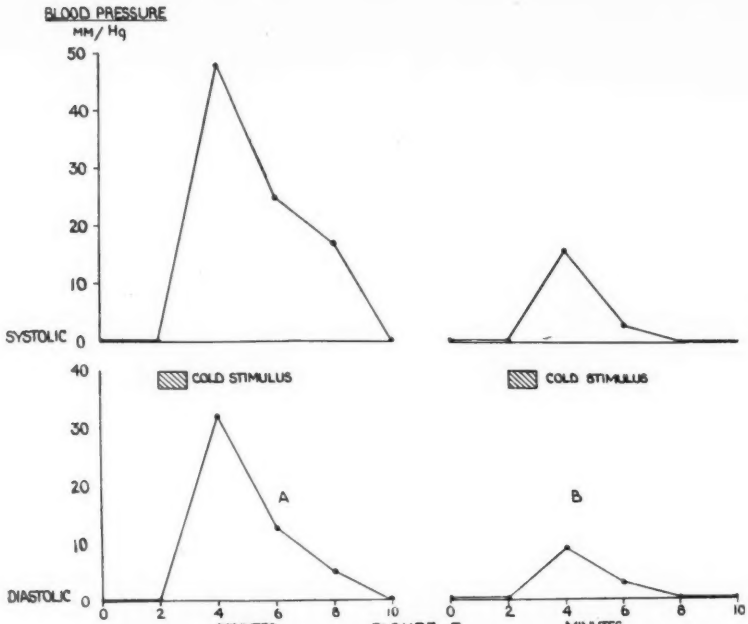

FIGURE 5

THE EFFECT OF HYDERGINE ON COLB PRESSOR TEST IN MALIGNANT HYPERTENSION
(AVERAGE RESPONSE OF 3 CASES)

A COLD PRESSOR RESPONSE BEFORE HYDERGINE

B COLD PRESSOR RESPONSE ½ AN HOUR AFTER ADMINISTRATION OF 0·3MGM HYDERGINE BY INTRAVENOUS INJECTION

Results of Treatment

(*a*) *While in hospital*

(1) *Effects on blood pressure.* This will be seen from consideration of Table I. In all cases there was some drop in blood pressure as compared with the reading prior to treatment and that during administration of the inert substance. The drop in pressure was considered to be significant in 12 cases, in whom the fall in diastolic pressure was greater than 14 mm. Hg as compared with the inert control period. The drop in pressure while on the inert substance was never more than 10 mm. diastolic, as compared with the previous period.

The 5 cases that did not respond in a significant fashion had poor renal function in four instances, and of these, 3 showed marked retinal and peripheral arteriosclerosis and the other (Case 1) was aged 25 years and had chronic nephritis. The case with normal renal function was markedly arteriosclerotic. None of these had shown a fall of over 18 mm. systolic and 10 mm. diastolic during the intravenous test dose.

(2) *Effect on symptoms.* Symptomatic improvement was noted in 13 cases, and in 10 of these complete relief of symptoms was observed. In no case were the symptoms aggravated, although three showed no change in the symptoms, and one had no symptoms.

Of the three cases who obtained no relief of symptoms, two were mentally unstable, and the other had severe side-effects.

The symptoms that were relieved consisted of tiredness and headache in all instances. Palpitation was present in four patients; of these, one noted relief with either hydergine or the inert

TABLE I

THE EFFECT OF TREATMENT WITH HYDERGINE UPON THE BLOOD PRESSURE AND SYMPTOMS, DURING THE HOSPITAL PERIOD

Case	Symptoms	Average daily blood pressure readings at rest		
		Before therapy	Inert control	Hydergine
1	Relieved	214/132	216/132	206/126
2*	Relieved	176/116	176/118	162/100
3*	Relieved	154/106	146/106	130/90
4*	Not improved	186/124	170/116	150/100
5	Not improved	230/128	210/122	190/114
6	Not improved	230/110	226/108	228/100
7*	Relieved	164/108	160/104	144/86
8*	Relieved	182/110	180/112	162/94
9*	Relieved	180/130	170/122	150/102
10	Improved	236/136	228/126	214/120
11	Improved	230/138	236/140	214/132
12*	Improved	266/144	246/140	200/110
13*	Relieved	186/112	182/110	152/88
14*	Relieved	222/130	214/126	154/90
15*	No symptoms	162/110	168/108	134/86
16*	Relieved	154/106	160/104	142/88
17*	Relieved	210/124	214/120	182/102

* Cases showing a drop of more than 14 mm. in diastolic pressure on treatment, as compared with the control period readings.

preparation and 3 with hydergine alone. When complete relief was obtained in 10 cases, it was noted that such relief was not obtained during the period of dosage with the inert control.

In Case 12, who had malignant hypertension at the age of 44, repeated intensely severe headaches associated with vomiting and hypertensive crises had been a feature before admission. This patient believed such headaches could be partially relieved by intramuscular femergin. Two such crises occurred while she was under observation in the ward before treatment was begun, and in both she was severely ill, the diastolic pressure rising to 180 mm. on one occasion and 172 mm. Hg on the other. During a crisis, intravenous injection of 0·6 mg. hydergine had little effect; intravenous injection of 40 mg. of pentamethonium iodide resulted in rapid reduction of headache and cessation of vomiting for a period of six hours, together with a fall in blood pressure to 130 mm. diastolic. Following treatment with hydergine, however, this patient had no further crises during her period of fourteen weeks in hospital. No relief was obtained during the two crises observed by the parenteral use of femergin.

(3) *Effects on the retinæ.* It is difficult to state what were the real effects on the retinal picture. There is no doubt that in cases with marked spasm of the arterioles (Cases 2, 4, and 12) such vessels were less spastic on treatment than before it. In Case 4, a recent hæmorrhage was noted on admission and a further one occurred within four days. On starting treatment, retinal spasm disappeared, and no further hæmorrhage or exudates occurred during the next month.

On the other hand, several hæmorrhages occurred during therapy in Case 12, where papillœdema was also present, and which gradually regressed during the period of observation of 14 weeks.

(4) *Renal function.* No significant change in renal function was noted as indicated by the urea range test.

(5) *Electrocardiogram.* Left ventricular hypertrophy was present in 10 subjects. No significant change in the 12-lead electrocardiogram occurred during treatment.

(6) *Heart size.* No significant changes were noted radiologically.

(7) *Side-effects.* The following side-effects observed were:

(*i*) *Nasal congestion.* This was common, and occurred on treatment in 12 subjects. Of

these, 7 experienced the sensation during the intravenous test. In only one, however, was it severe enough to cause discomfort (Case 4). This symptom was transient, lasting 3–6 days in nine subjects and in three it persisted for 14 days and was present on discharge from hospital.

(*ii*) *Nausea.* This occurred in three subjects and was relieved by reduction of therapy in two, and in none was it caused by the inert preparation. In these two subjects, nausea was maximum one hour after intramuscular injection. In one patient (Case 4) nausea was severe and accompanied by lassitude, pain behind the eyes and vomiting, following discharge from hospital, even in as small a dose as 10 minims t.i.d. Vomiting did not occur in any case while in the hospital, however.

(*iii*) *Drowsiness.* This was noticed in a mild form by five subjects during treatment; three others, while not drowsy, volunteered the information that they slept much better during treatment. There were no such effects during therapy with the inert preparation.

(*iv*) Slowing of the pulse rate occurred in 13 subjects while on treatment, by 10–20 beats a minute.

(*b*) *Out-patient treatment.*

In all subjects, following discharge from the ward, oral therapy was continued for one month in a dose of 35 minims t.i.d. by mouth. For the following month subjects were given a similar dose of the inert preparation, unknown to them, and then all treatment was stopped for a further month. After this, continued dosage with the active preparation was resumed.

(1) *Effects on blood pressure.* Of the 17 cases observed, the blood pressure was significantly lower on the hydergine treatment than on the inert preparation or on no treatment in 12 instances. Of the other 5, one was arteriosclerotic (Case 5) and emotionally unstable. Another (Case 10), had marked peripheral and retinal arteriosclerosis. Case 4 could not continue treatment on account of side-effects. Case 6 is of some interest. She was emotionally unstable and proved at follow-up to be quite unreliable. Her many symptoms were relieved equally by hydergine and the inert preparation. She did not trouble to procure a suitable measure for the hydergine and had by way of compromise take three tablespoonfuls a day for a period of two weeks. This was a dose of 42 mg. a day. No ill effects of over-dosage resulted in this arteriosclerotic subject. Case 1 also failed to respond satisfactorily.

(2) *Effects on symptoms.* Case 1 was symptom-free at home on treatment and was able to take up light work in a garage. On ceasing treatment after four weeks, he became depressed, tired, and had severe headaches, which were not relieved by treatment with the inert preparation but which disappeared with the active one. Case 2 felt better and less tired on treatment, but could do a full day's work as a housewife with two young children whether on treatment or not. Case 3 worked on treatment as a night sister in a hospital—work which she believed herself incapable of doing before admission. On the inert preparation, she felt tired and was subject to palpitation (extra-systoles) and felt like giving up her job. When treatment was renewed, so apparently was her vigour. Case 4, who had nausea and nasal congestion in the ward, did not do well. On full doses at home, he developed headache, nausea, vomiting, pain behind the eyes and was " dead-beat " and unfit for anything. On stopping treatment, he became reasonably well again, apart from his morning headache. He had no such side effects on the inert preparation, but on returning to treatment on a smaller dose of 10 minims t.i.d. he again had these symptoms, and therapy was stopped. Cases 5 and 6 were unreliable on account of their emotional instability. Case 7 became symptom-free at home on treatment but not on the control. Case 8 responded similarly. Case 9 returned to full work and had no complaints apart from coldness and stiffness in the right hand, much relieved by physiotherapy. Case 10 was better on both inert and control preparations; he was a very anxious, worrying man who, when given confidence improved greatly, but had many symptoms while off all treatment. Case 11 did not return to full work and two months after discharge developed renal failure. Case 12, who had malignant hypertension, stated that she felt very well for four months after treatment during which she led a lazy life and had no further head-

ache. Case 13 had no complaints, doing energetic housework on hydergine, but developed headache and tiredness on the inert preparation. Case 14 remained symptom free on treatment, but complained of tiredness and lack of interest in her housework while on the control or no treatment. Case 15 had no symptoms before, during, or after treatment. Case 16 returned to work as a policeman on the beat feeling well during treatment apart from tiredness while on night work. Case 17 continued work in a bus company and, apart from old-standing fibrositis of the neck and shoulders, remained well on treatment; he has only been followed up for three months.

(3) *Effects on the retinæ.* In no case was there advance in the degree of spasticity of the retinal vessels, and in no case did exudate or hæmorrhage appear, although these had been previously present in Case 4, in whom an acute progressive arteriolar change had at least been halted. In Case 12 papillœdema had practically disappeared after three months.

(4) *Effects on electrocardiogram and heart size.* None of significance were noted.

(5) *Side-effects.* Nasal congestion present at discharge from hospital in three cases, disappeared within one month in two of them. In Case 4 it persisted as long as treatment was given.

Summary and Conclusions

The effect of intravenous injection of 0·3 mg. of hydergine in 50 hypertensive patients was to lower the blood pressure to a varying extent in each instance. As a result of this survey the impression was formed that those subjects with minimal peripheral arteriosclerosis and good renal function were most liable to show a satisfactory response. The most marked response was seen in three subjects with malignant hypertension and good renal function.

Reduction of the pressor response to cold is an interesting feature and in keeping with the results of von Kappert (1947) and Freis *et al.* (1949). Whatever the initial lability of the blood pressure before hydergine was administered, the average response to the cold pressor test following injection was diminished and readings showed a rise of some 15 mm. systolic and 10 mm. diastolic half an hour after injection. From this it is reasonable to suggest that hydergine may be expected to prevent the transient rises of pressure to which hypertensive subjects are liable, and further, to prevent repeated hypertensive encephalopathy in certain subjects; such prevention did in fact occur in the one subject with malignant hypertension who received a therapeutic regime.

No catastrophic fall in pressure did occur during injection even with reduction of injection time to 30 seconds. Further, nasal congestion was the only side-effect noted after injection and presumably due to stellate ganglion block. " Opening up " of spastic retinal arterioles was noted in 11 cases, within ten minutes of intravenous injection.

Combined oral and parenteral therapy resulted in a significant fall in diastolic pressure in 12 subjects, all of whom had good renal function and minimal arteriosclerosis.

Relief of symptoms of headache and tiredness and palpitations occurred during treatment in 13 subjects and in 10 was complete; in none of these 10 was there similar relief while taking the inert preparation. Hydergine probably increases cerebral blood flow by its vasodilator action and the reduction of headache may be related to this action.

Side effects were only unpleasant enough in one subject to result in cessation of therapy; in this subject nausea and vomiting were present even when small doses were being given and the symptoms were considered to be due to excitation of the vomiting centre, similar to that which occurs in ergot poisoning. Drowsiness, present in 5 subjects, was mild and could be associated with central nervous depression. Nasal congestion, as mentioned, was considered to be a sign of stellate ganglion block, and was the commonest side-effect, occurring in 12 out of 17 subjects; it was noted by Bluntschli and Goetz (1947) and repeatedly since then by other authors. The slowing of heart rate as noted by Rothlin (1944) was shown to be partly inhibited by atropine by Wilkins *et al.* (1949). This slowing may be due to the property possessed by ergot alkaloids of inactivating cholinesterase; it is possible that it is due to central nervous depression.

Follow-up of the 16 benign cases demonstrated that 10 of the 11 subjects, with good renal

function and a labile pressure and minimal arteriosclerosis, were able to do a full day's work and maintain a lower blood pressure on therapy than that recorded while on no treatment or on the inert preparation; further, none showed advance of retinopathy. The diastolic pressure was maintained below 90 mm. in three subjects at rest, who were leading active normal lives.

It would seem justifiable on the evidence of this preliminary observation to investigate the potentialities of these dihydrogenated derivatives or ergot further by clinical trial. Probably most subjects can take a larger dose than that used in this survey although this may not be desirable. Hydergine does not remove the cause of hypertension. The reduction of pressure obtained in the treated cases did not, over this short period of follow-up, cause harm to any subject. If such reduction can be maintained over a period of years, the increased bodily wear and tear to which hypertensive subjects are liable may be reduced. Further, if the acute progressive phases of hypertension can be prevented in younger subjects, then benefit may be said to have been obtained.

Comparison with the results of surgical sympathectomy as a method of treatment can only be made when a larger number of subjects have been followed up over a period of years.

The results of this clinical trial do not prove that hydergine acts entirely by producing adrenergic blockade in man. It is still possible that at least some of the effects observed were due to central nervous depression and elucidation of this point will be of the utmost interest.

I wish to express my thanks to Dr. A. Rae Gilchrist for permission to publish these cases and for his advice and encouragement in the preparation of this paper; to Messrs. Sandoz for supplies of hydergine and technical advice, and to Mr Shepley, University Artist, Department of Surgery, University of Edinburgh, for his skilful preparation of the diagrams.

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ANEURYSM OF THE CORONARY ARTERIES

BY

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Aneurysm of the coronary arteries is rare. Since the first case in 1812 up to the review by Scott in 1948, 47 cases of localized aneurysm have been reported. Two further cases are described below.

Case I

A retired butcher, aged 66, gave a history of increasing breathlessness for one year. He also had occasional sharp pain in the chest, not typically anginal.

On examination, he was cyanotic and orthopnœic and had consolidation of the upper lobe of the right lung, with bilateral basal crepitations. No clinical abnormality was noted in the heart, but an X-ray was reported as showing cardiac enlargement. Three days later his dyspnœa had increased and he complained of severe pain down both arms and across the chest. His blood pressure at this time was 100/65; he had

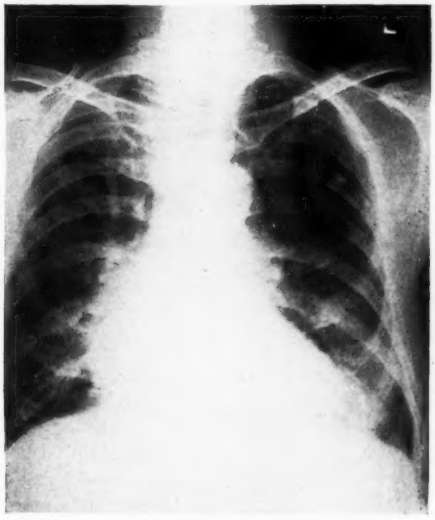

FIG. 1.—Case 1. X-ray showing the outline of the blood clot over the right atrium.

œdema over the sacrum and a blood count showed 13,700 white blood corpuscles with 79 per cent polymorphs. His W.R. and Kahn tests were negative. He was thought to have had a further coronary thrombosis with increasing heart failure, and he died the next day.

Post-mortem examination. The pericardium was lightly adherent over the whole heart. Over the

posterior surface of the right atrium there was a small blood clot showing early organization. The heart weighed 615 g. The muscle was pale and friable. There was a small thrombus attached to the commissure of the two posterior cusps of the aortic valve, apart from which the cusps were normal. Immediately above the aortic valve there were two small saccular aneurysms of the aorta, which bulged posteriorly and upwards. The larger was 3·7 cm. in diameter; the smaller was adjacent to the larger with a strip of atheromatous aorta between. The rest of the aorta showed only slight atheroma. The left coronary artery, the first part of the circumflex branch and of the descending interventricular branch were completely obliterated by calcifying atheroma. The right coronary artery was hypertrophied, and 0·6 cm. from its origin there was an aneurysm 1·9 cm. in diameter partly filled with old laminated clot. There were a few ounces of fluid in the right pleural cavity, œdema particularly of the right lung, and some recent adhesions over the right apex. The liver showed chronic passive venous congestion.

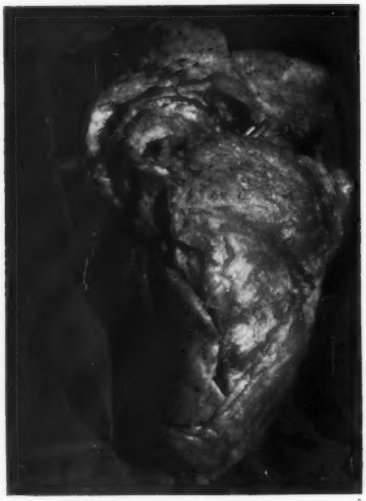

FIG. 2.—External view of the heart from Case 1 with diagram.

FIG. 3.—Internal view of the left ventricle and aorta from Case 1, showing the site of the aortic aneurysm.

Histology. The wall of the left ventricle showed hypertrophy of muscle fibres, and patchy diffuse fibrosis. There were also areas of more recent necrosis with polymorph reaction. The aneurysm of the ascending aorta appeared to originate in an area of necrosis of the media. The walls were formed by collagen from the adventitia, and were lined by clot and fibrin. In the aorta adjacent to the aneurysm there was extensive vascularization of the outer third of the elastica, and perivascular infiltration with lymphocytes. The wall of the coronary aneurysm consisted of collagen only, with perivascular round cell infiltration.

Case II

A doctor's widow, aged 82 years, felt ill at supper, following a car drive in the afternoon, and retired to bed. In the morning she said that she had a " bad night." During the day she collapsed and the doctor was called but on arrival found her dead.

Her son said that his mother had suffered from a weak heart for 50 years and that recently her heart attacks had been worse. She had moved several times and only one doctor who had attended her could be found. The only information he could give was that she had had a retinal hæmorrhage and that she complained of dyspnœa on exertion and occasional œdema of the ankles.

Post-mortem examination. No abnormality was found in the respiratory and alimentary tracts. The liver showed moderate fatty change. The spleen was normal. The kidneys showed a slight reduction in the cortex with occasional small scars and cyst formation, the small arteries were prominent and the capsule did not strip very readily, the surface left being finely granular. The picture was that of renal arteriosclerosis.

The heart was 20 cm. long, 12 cm. across at the auriculo-ventricular sulcus and 10 cm. thick. It weighed 460 g. The left atrium had projecting from it a globular mass 6×7×6 cm. over which the pericardium was attached by fibrous tags. This mass had a wall 2 mm. thick, which obviously consisted of layers, some patches being yellow. Inside was firm laminated clot, mainly yellow, but with occasional hæmorrhagic places. On section the myocardium of the left ventricle was 18 mm. thick while that of the right was 8 mm. thick. The wall of the left ventricle showed a number of small white infarcted areas. The tricuspid valve was 11·5 cm. in circumference and the pulmonary 7 cm., both appearing normal. The mitral valve (9 cm. in circumference) was thickened with shortened chordæ tendineæ and under its posterior cusp just inside the left ventricle was a calcified mass. The aortic valve was much thickened and was 7 cm. in circumference. Attached to the posterior and medial angle of the left atrium was a dark reddish-brown almond shaped ante-mortem clot, 3·5×1·5 cm. No other abnormality was found in the left atrium. The orifices of the coronary arteries were very large, being about 1 cm. in diameter on either side. Each had a patch of atheroma round the mouth. Both coronary arteries were much dilated and tortuous and the site of well developed

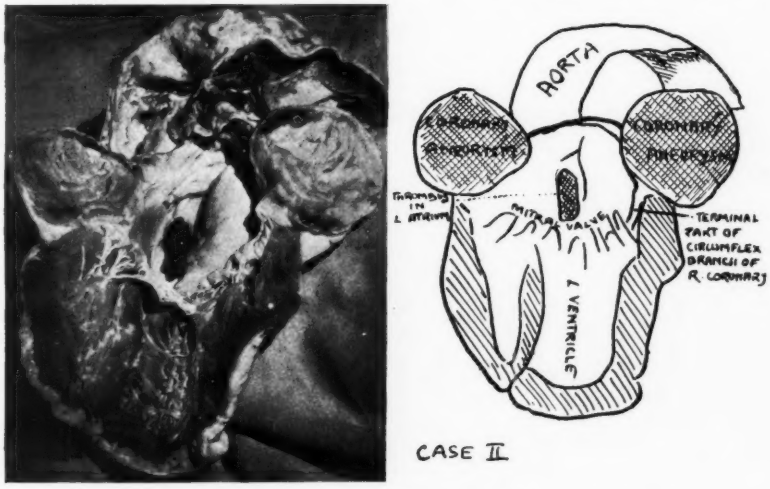

FIG. 4.—Anterior view of the heart from Case 2 showing the large coronary aneurysm.

atheroma. Their average circumference was about 2 cm. The left coronary took a normal course; so did the right until, at the point where the circumflex branch turned down, on the back of the left ventricle, just inferior and posterior to the aortic valve, it entered a small saccular atheromatous aneurysmal cavity about 2 cm. in diameter, containing no clot. From this sac sprang a completely calcified non-patent artery which penetrated the muscle of the left ventricle and traversing it, appeared just under the posterior cusp of the mitral valve as the calcified mass previously mentioned. From here it ran laterally and anteriorly curving round the ventricle under the posterior mitral cusp to end in the inferior-medial wall of the large aneurysm. No other vascular attachment of the large aneurysm could be found and it "shelled off" the left atrium with ease except where the calcified vessel entered.

Histologically the large aneurysm contained laminated clot. The wall showed marked atheromatous change, much fibrosis with cholesterol clefts, scanty frayed elastic tissue, patches of calcification and a few collections of small round cells. The vessel under the mitral valve was completely calcified and its previous microscopical structure as an artery could just be discerned.

The aorta showed little atheroma in the ascending part but there was severe atheroma in the arch and descending parts, patches of which were breaking down. The lower part of the descending aorta where it bifurcates was occupied by a large aneurysm $12 \times 8 \times 5$ cm containing a very firm yellow, hæmorrhagic clot. Near its upper pole the aneurysm had ruptured filling the retroperitoneal space with a vast quantity of blood and causing the woman's death.

Discussion

Scott in 1948 collected 47 cases of coronary aneurysm of which 15 were congenital, 12 mycotic-embolic, 6 syphilitic, 6 arteriosclerotic, 4 of other types, and 4 unclassified. He considered that these aneurysms were localized or diffuse, and that all the diffuse aneurysms were congenital while the localized had various origins. He found that in cases of localized aneurysm the left coronary was more frequently involved. Men were more often affected than women, and there were no pathognomonic clinical findings. The condition was frequently associated with cardiac infarction.

In our first case, arteriosclerosis and syphilis were considered as possible ætiological factors, the negative W.R., the history, and the age of the patient favouring the former diagnosis and the appearance of the aortic aneurysm and some parts of the histological picture favouring the latter. A suggestion that the aortic aneurysm resulted from an avascular necrosis, due to occlusion of the left coronary artery, from branches of which the root of the aorta partly derives its blood supply, was not supported by much evidence. Radiographs of the coronary arteries injected with bismuth in gelatin showed the root of the aorta to be one of the areas where there was a particularly rich anastomosis between right and left coronary arteries (Shillingford, 1950).

In our second case the lack of clinical data made it difficult to prove the cause of the aneurysms but the appearances post mortem strongly supported an arteriosclerotic origin. This was favoured by the presence of coronary and myocardial degeneration and by severe arteriosclerotic changes in the aorta particularly the abdominal part terminating in its rupture. The case was unusual in several features; it occurred in a woman, the right coronary was affected and there was more than one aneurysm.

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AN EXERCISE TEST IN INTERMITTENT CLAUDICATION

BY

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In most cases of intermittent claudication the diagnosis is apparent after the history and clinical examination have been completed. Although the history itself may be misleading, clinical examination is usually fruitful; the signs of obliterative arterial disease are present in most, and cases of anæmia and coarctation of the aorta that present with intermittent claudication should be easily diagnosed. However, in a number of cases the diagnosis remains doubtful. André-Thomas and Levy-Valensi (1918), and André-Thomas (1922) found in patients with intermittent claudication a diminution in oscillometric pulsations after exercise. Comroe (1923) finding a diminution in the peripheral pulses of intermittent claudication patients after exercise, believed that arterial spasm might be responsible even in the absence of obliterative arterial disease. Pearl (1937) reported six cases showing a similar phenomenon. Similar cases have been reported by Leary and Allen (1941) and by Lindqvist (1945*a*, 1945*b*). The latter stressed the value of oscillometry after exercise in diagnosis; he believed that the diminution in pulsations which he found was evidence of vascular spasm, rather than a sequel of obliterative arterial disease, implying a functional rather than an organic lesion. Arterial spasm itself as a source of pain in intermittent claudication was denied by Lewis *et al.* (1931); Leriche (1937) and Ejrup (1948) further supported Lewis's view, as do our findings.

In 1944 Ejrup published an account of an instrument which after modification he considered would act as a tonoscillograph; he defined this as an instrument for measuring and recording variations in the pulsations and pressure in a vessel (Ejrup, 1948). His apparatus has the advantage of enabling continuous recordings to be made both before and after exercise. He studied the appearances of tonoscillographic tracings obtained before and after exercise in normal subjects and in those with intermittent claudication. Normal subjects showed an increase in the magnitude of pulsations and an apparent increase in blood pressure after exercise. Cases of intermittent claudication showed a decrease in the magnitude of pulsations after exercise, and an apparent fall in blood pressure distal to the site of arterial obstruction in the affected limbs. This phenomenon Ejrup termed the "inverse reaction." He also found the inverse reaction in some cases of anæmia (Ejrup, 1949), and of coarctation of the aorta; the inverse reaction was not found in cases of Raynaud's syndrome.

The following is an account of normal persons, patients with intermittent claudication, and those with pain in the leg due to other causes than obliterative arterial disease, studied with Ejrup's tonoscillograph before and after exercise. This investigation was made to evaluate tonoscillography after exercise in the diagnosis of intermittent claudication due to obliterative arterial disease, to correlate tonoscillographic and arteriographic findings, and to determine whether tonoscillography after exercise could be used in place of arteriography in the location of arterial obstruction. We further wished to discover whether the inverse reaction could be recognized clinically.

Apparatus

The apparatus is an automatic oscillograph. A cuff placed around the limb is automatically inflated and deflated with compressed oxygen, and pulsations in it during the inflation phase are

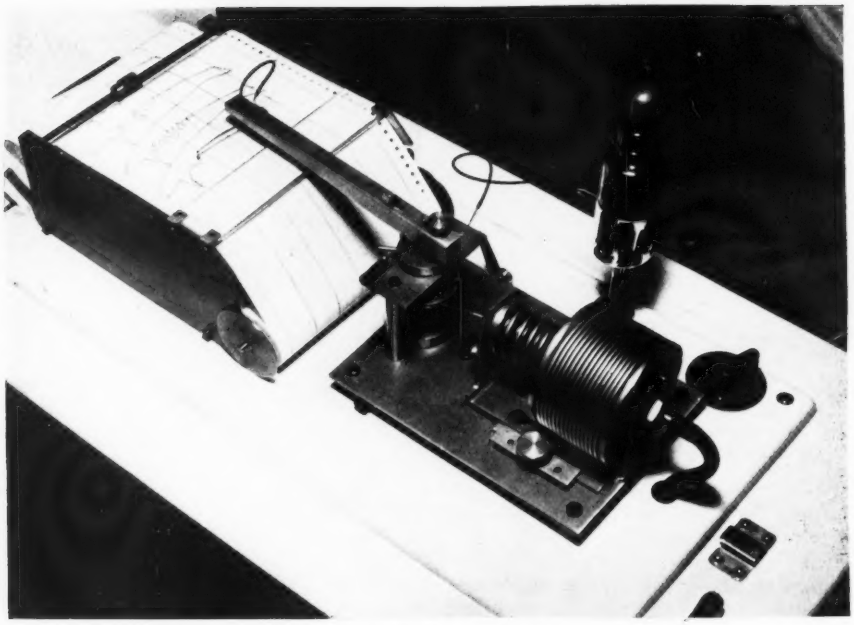


FIG. 1.—Ejrup's tonoscillograph. The writer is shown advancing vertically during the inflation phase, and recording pulsations in the horizontal direction.

transmitted, by means of a piezo-electric manometer and an amplifier, to a pen (Fig. 1). As the pressure increases the pen advances vertically and pulsations are recorded in the horizontal plane. The recording paper is marked with horizontal lines, and the apparatus calibrated so that these mark the pressure increase in the cuff in steps of 50 mm. Hg from 0 to 300 mm. A tracing is automatically obtained every 30 seconds.

METHODS

Examinations are always made in the same room which varies only slightly in temperature (18°–22° C.). Before examination patients rest undisturbed on a rubber mattress for at least thirty minutes. The cuffs used (Fig. 2) are of three different sizes, varying in width and length. Each consists of an inflatable rubber ring surrounded by a firm cloth covering. On the outside of the latter is a row of numbered metal rungs, and on the end a hook. The cuff is tightly secured by engaging the hook on a rung.

The same rung is used in readings before and after exercise and the tightness of the cuff is thereby kept the same. The different sized rubber rings measure approximately 25×8 cm., 32×10 cm., and 61×10 cm. The smallest of the cuffs which will encircle the limb at the site being examined is used.

Recordings are made at three different levels of the limb; at the ankle, the calf, and the thigh. At the ankle the cuff is placed so that its lower border is level with the upper end of the medial malleolus. At the calf it is placed so that the middle of the cuff lies between the knee joint and the thickest part of the calf. At the thigh the middle part of the cuff is made to lie around the thinnest part of the thigh above the knee. Its lower edge then coincides with the upper margin of the patella.

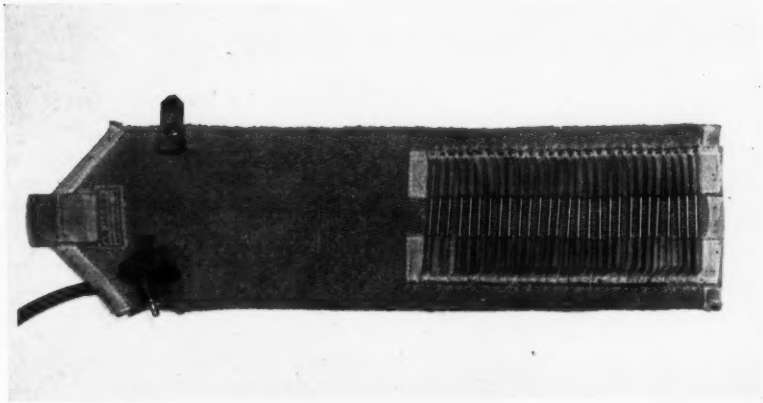


FIG. 2.—Cuff with numbered metal rungs. The inflatable rubber ring is on the inner side of the cloth covering.

In cases where the recording at the ankle is normal a tracing may be made at the foot; though owing to the shape of the foot and the difficulty in obtaining close apposition of the cuff to it, this is not always satisfactory. In cases of extensive arterial obstruction there may be insufficient pulsations to give satisfactory tracings, even with a high degree of amplification.

Following the practice of Ejrup (1948) recordings are first made at rest and the amplification adjusted so that the maximum horizontal deflection measures approximately 8 mm. Experience has shown that this is the most satisfactory size of deflection. Two to four tracings are taken and the recording stopped. After tracings have been taken at rest the subject exercises. We have tried various methods of exercise for patients, including running and walking in a corridor, walking on a moving belt, using the limb to work an ergometer, and repeated dorsiplantar flexion of the foot with the leg in the horizontal position. The following are considered to be the most satisfactory types of exercise and have been adopted: for recordings from the thigh, calf, and foot the subjects if possible run slowly, or alternatively walk briskly, for up to 744 feet. This distance is usually covered in about 120 seconds. Sometimes the development of pain prevents their reaching this distance. In subjects who are unable to walk, dorsiplantar flexion of the foot at the rate of once a second for up to 90 seconds is performed, with the leg horizontal. This has been found to be sufficient exercise for ankle and foot tonoscillography. Control subjects never performed less exercise than patients with intermittent claudication.

After exercise the subject immediately lies down again, and a series of further tracings is commenced, care being taken to ensure that the lag period between the end of exercise and the start of the first tracing is never more than thirty seconds (see below). The subject rests undisturbed for thirty minutes between the end of a recording after exercise and the commencement of the next.

In attempting to elicit the inverse reaction clinically, subjects rest as above, and the dorsalis pedis and posterior tibial pulses are palpated. If these are present, dorsiplantar flexion of the foot is performed, as described for tonoscillography. Immediately after this exercise the dorsalis pedis and posterior tibial arteries are again palpated, and disappearance or diminution in their pulsations noted.

SUBJECTS

Three groups of subjects were studied:

(1) 42 normal subjects,

(2) 4 patients with pain in the leg not due to obliterative arterial disease,

(3) 53 patients with intermittent claudication due to obliterative arterial disease; in 27 patients in this group femoral arteriograms or aortograms were performed.

RESULTS

Group 1. *Normal subjects.* Tonoscillography before and after exercise, as described above, was performed on forty-two subjects without symptoms of intermittent claudication, and without signs of peripheral vascular disease or any condition which might cause such pain. Ninety tonoscillograms after exercise were performed on these subjects. On comparing the magnitude of pulsations in the first or second tracing after exercise with those taken at rest the large majority showed an increase; the remainder showed no change. The level of pressure in the cuff at which the pulsations disappeared was higher or remained unchanged (Fig. 3). The relation of pulsations to possible blood pressure changes in the limbs will be considered more fully below.

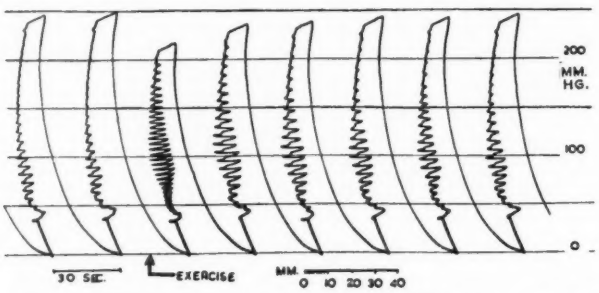


FIG. 3.—Tonoscillogram from right thigh of normal subject, showing increase in the magnitude of pulsations after exercise.

Some normal subjects show a decrease in the magnitude of pulsations in the first tracing after exercise. This phenomenon will be further considered later.

Group 2. *Patients with pain in the leg not due to obliterative arterial disease.* Four patients who were referred for investigation of pain in the leg, and in whom a diagnosis of intermittent claudication due to obliterative arterial disease was not made, form this group.

Case 1. *M.B., man, aged* 46 *years.* A poor witness, who gave a history of nine months' pain in the left leg, suggestive of intermittent claudication. There were no objective clinical or radiological signs of obliterative arterial disease, nor of any condition that might cause intermittent claudication. Varicose veins were present in the left lower leg. Femoral arteriography showed normal arteries throughout the left leg. Tonoscillography after exercise was completely normal. The pain in this man's leg was considered to be due partly to his varicose veins, and partly to psychogenic causes.

Case 2. *H. L., man, aged* 49 *years.* History of ten months' pain in the right leg which was considered to be suggestive of, but probably not, intermittent claudication. He had had poliomyelitis when aged three years. There were no objective clinical or radiological signs of obliterative arterial disease, nor of any condition that might cause intermittent claudication. There was wasting and shortening of the left leg from old poliomyelitis. Femoral arteriography showed normal arteries throughout the right leg. Tonoscillography after exercise was completely normal. The pain in this man's leg was considered to be connected with a grossly abnormal gait following poliomyelitis.

Case 3. *H.H., man, aged* 40 *years.* History of twelve months' pain and weakness in the legs, which was considered to be suggestive, but probably not, that of intermittent claudication. There were no objective clinical or radiological signs of obliterative arterial disease, nor of any condition which might cause intermittent claudication. Femoral arteriography showed normal arteries throughout the right leg. Tonoscillography after exercise was completely normal. This patient subsequently developed symptoms and signs of prolapse of the intervertebral disc between the sixth and seventh cervical vertebræ; it is considered possible that the pain in his leg may be related to the latter condition.

Case 4. *M.B., woman, aged* 35 *years.* A poor witness, who gave a history of two years' pain in the legs, suggestive of intermittent claudication. There were no objective clinical or radiological signs of obliterative arterial disease, nor of any condition that might cause intermittent claudication. Femoral arteriography

showed normal arteries throughout the right leg. Tonoscillography after exercise was completely normal. No cause has been found for the pain in this patient's leg, but her unreliability as a witness has been increasingly apparent on repeated visits to hospital, also her tendency to symptoms of psychoneurotic ill-health.

In all these four patients clinical and radiographic evidence was against a diagnosis of intermittent claudication due to obliterative arterial disease, and the findings on tonoscillography after exercise were those of normal subjects

Group 3. *Patients with intermittent claudication due to obliterative arterial disease.* Tonoscillography before and after exercise was carried out in fifty-three patients in this group. In twenty-seven of these patients the diagnosis of obliterative arterial disease was confirmed by arteriography or aortography. On the fifty-three patients 288 tonoscillograms after exercises were recorded.

In all cases of intermittent claudication there was a decrease in the magnitude or a disappearance of pulsations compared with those obtained at rest (inverse reaction). This lasted at least during the first two tracings after exercise and was found at a definite level in the limb and persisted distal to that site (Fig. 4). Pulsations may not return to their amplitude before exercise for as long as thirty minutes, and disappear at a lower level of pressure in the cuff.

There was good correlation between the site of the obstruction demonstrated by arteriography and the level of the inverse reaction, which was present distal to gross narrowing or obstruction of a vessel. Thus of seven cases with gross narrowing or obstruction of the aorta or iliac arteries, six showed inverse reactions at the thigh level and below; while in the remaining case it was not possible

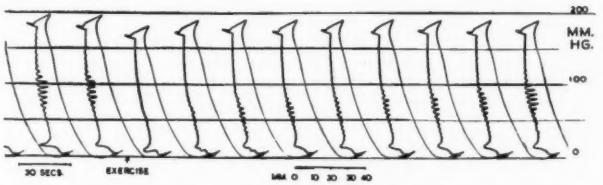


FIG. 4.—Tonoscillogram from right ankle of patient with intermittent claudication due to obliterative arterial disease, showing a decrease in the magnitude of pulsations after exercise.

to record any pulsations in the limb at all. Twenty cases on arteriography showed the limb vessels to be affected; in fourteen there was complete obstruction of a major vessel, and in six gross narrowing. The femoral artery was completely obstructed in ten of the fourteen (Cases 1, 3, 12, 13, 15, 16, 22, 23, 29, 31); all, except one (Case 29) of these showed inverse reactions at the level of the calf and distally. This exception showed normal reactions after exercise at the thigh and calf, and an inverse reaction at the ankle. Cases 3 and 12 showed in addition an inverse reaction at the thight. In Case 12 the inverse reaction at the thigh was of much shorter duration than in cases with aortic or iliac artery obstruction. Case 3 had a much less easily felt femoral pulse on the affected side, suggestive of an additional obstruction proximal to the femoral artery. Three (Cases 8, 44, 46) showed complete obstruction at the level of the popliteal artery, but not above; these showed inverse reactions at the ankle. Case 5 showed complete obstruction of one of the lower leg arteries, the anterior tibial, in the absence of more proximal complete obstruction; an inverse reaction was found only at the foot.

In six (Cases 6, 28, 34, 35, 37, 39) there was narrowing of the limb arteries without complete obstruction; in one of these (Case 28) where the femoral artery only was affected, inverse reactions were found at the thigh level and distally. As in Case 12 the inverse reaction at the thigh was of much shorter duration than in cases with aortic or iliac artery obstruction. Case 35 showed narrowing of the femoral, popliteal and lower leg vessels: inverse reactions were present at the calf and ankle. In three (Cases 6, 34, 19) the femoral and lower leg vessels were affected; one (Case 39) showed inverse reactions at the ankle and foot (recordings were not made at the calf and thigh),

another (Case 6) at the ankle, and the third (Case 34) at the foot only. In Case 37 only the posterior tibial artery was affected; an inverse reaction was present only at the foot.

Fig. 5 and 6 show the relation between tonoscillography after exercise and arteriography in all cases in which both examinations were made. A recording at the foot was usually only made in those cases in whom a normal reaction after exercise had been found at the ankle. In Cases 13 and 15 there were insufficient pulsations to record at the ankle and foot. In Case 39 recordings were not made at the thigh and calf. Cases in which aortography was performed are not included in Fig. 6.

Clinical Determination of the Inverse Reaction. In fifteen patients of Group 3 (intermittent claudication due to obliterative arterial disease), in whom the dorsalis pedis and posterior tibial arteries were palpable at rest, pulsations in these vessels were examined before and after exercise, as described above. All but two of these patients showed a diminution or absence of pulsations after exercise, comparable to the inverse reaction on tonoscillography after exercise, but often of shorter duration.

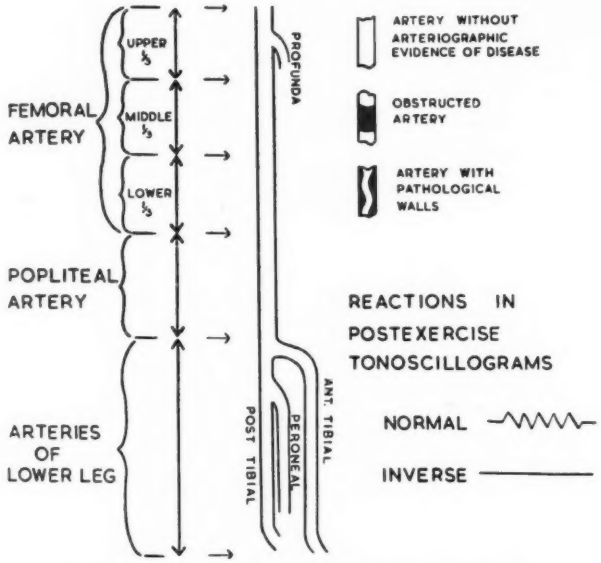


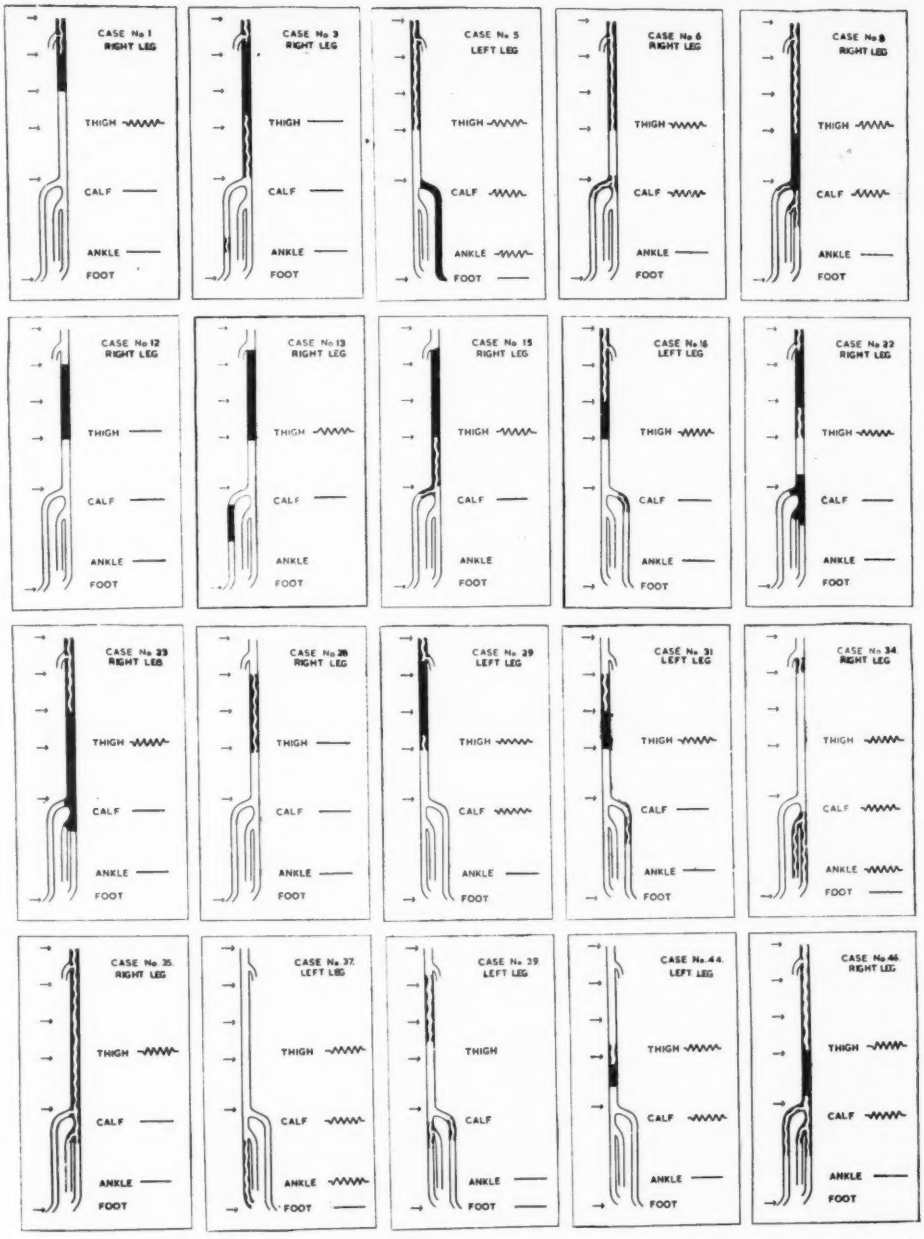
FIG. 5.—Key to diagrams comparing arteriographic and tonoscillographic findings.

DISCUSSION

The Diagnosis of Intermittent Claudication due to Obliterative Arterial Disease. Ejrup (1948) described the inverse reaction as an invariable finding in patients with intermittent claudication, compared with the response found in normal subjects. Our results show its relation to intermittent claudication in cases due to obliterative arterial disease.

This condition may present considerable difficulty in diagnosis; the history obtained may be inconclusive, the peripheral pulses at rest may be easily felt and nutritional changes in the limbs absent. Boyd (1950) pointed out the difficulty which the diagnosis of intermittent claudication presents in some cases.

Tonoscillography after exercise may be used as a simple method of confirming a clinical diagnosis


CASE No 1 RIGHT LEG
CASE No 3 RIGHT LEG
CASE No 5 LEFT LEG
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CASE No 8 RIGHT LEG
CASE No 12 RIGHT LEG
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CASE No 16 LEFT LEG
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CASE No 35 RIGHT LEG
CASE No 37 LEFT LEG
CASE No 39 LEFT LEG
CASE No 44 LEFT LEG
CASE No 46 RIGHT LEG
THIGH
CALF
ANKLE
FOOT

FIG. 6.—Comparison between arteriographic and tonoscillographic findings in 20 cases.

of intermittent claudication due to obliterative arterial disease. In all cases the tonoscillographic findings should be considered in conjunction with the clinical picture, as other painful conditions of the leg such as osteoarthritis may be present in addition to arterial disease.

The results of clinical examination of the peripheral pulses before and after exercise above show that the tonoscillograph is not always necessary to demonstrate the inverse reaction, but we have not elicited it clinically in all cases where it was shown on tonoscillography. A negative finding clinically is not therefore as reliable an indication of the absence of obliterative arterial disease.

The Location of Arterial Obstruction. Tonoscillography after exercise will approximately indicate the site of the upper level of an arterial obstruction (see Fig. 6). Thus in cases with obstruction of the aortic or iliac arteries inverse reactions were found at the level of the thigh and distally; in cases with femoral artery obstruction, at the level of the calf and distally; in those with popliteal artery obstruction, at the ankle and foot; and in those with obstruction of a lower leg artery, only at the foot. There was one exception to the above in the present series; Case 29, with a completely obstructed femoral artery, had a normal reaction after exercise at the calf level. In cases of intermittent claudication due to arterial disease where the obstruction is incomplete, tonoscillography is a less reliable indication of the site of the disease; but all such cases investigated by us showed an inverse reaction at some level in the affected limb. It should be emphasized that a normal response after exercise has never been found distal to the level at which an inverse reaction has been recorded. As the inverse reaction will be found throughout the leg distal to a block, no information is obtained about the lower level of the obstruction. Should direct arterial operations such as those described by dos Santos (1947), Holden (1950), Lian and Welti (1950), and Reboul and Laubry (1950) be planned, arteriography or aortography will be necessary to define the limits of the arterial obstruction. If one leg is symptom free tonoscillography after exercise will indicate the presence or absence of arterial disease in it. With these limitations tonoscillography after exercise offers, therefore, an alternative to arteriography, and is particularly useful where the latter is contraindicated.

Mechanism of the Inverse Reaction. This will await investigation by other methods. Observations have shown that it is essential that the muscles between the site of arterial block and the recording cuff are exercised. Thus dorsiplantar flexion of the foot, sufficient to produce ischæmic pain in the calf and an inverse reaction at the ankle in cases with femoral artery obstruction, has failed to produce an inverse reaction at the calf, where this has subsequently been recorded after walking or by exercising the thigh muscles only.

The development of the pain of intermittent claudication is not necessary for the production of an inverse reaction. It has been shown that pulsations, as recorded by this method, diminish in patients with intermittent claudication after exercise. It is not considered that a fall in blood pressure after exercise can necessarily be inferred from these tonoscillographic tracings. Ejrup (1948) considered that the blood pressure could be approximately measured from the range of pulsations, with a standardized 8-mm. deflection, and that there was a fall in blood pressure, as well as a decrease in the magnitude of pulsations as part of the inverse reaction. In all our cases of intermittent claudication (Group 3) there was an apparent fall in blood pressure in the limb on the tonoscillographic tracings after exercise, as compared to those at rest before exercise. This may not represent a true fall in blood pressure, owing to the method of estimating blood pressure from the tracings. If pulsations become much diminished or absent it appears to us that it will be impossible to measure blood pressure, unless it is assumed that pulsations and blood pressure alter pari passu. No evidence has been found for this.

The difficulty in attempting to measure blood pressure and blood pressure changes by this method has been demonstrated by recording resting tonoscillograms in normal healthy subjects, and deliberately varying the magnitude of pulsations from tracing to tracing by altering the amplification (Fig. 7). When pulsations are absent or very small, the end points of the pulse pressure range and the systolic and diastolic blood pressures are difficult if not impossible to determine.

Ejrup's method might be more accurately described as oscillography after exercise than as

tonoscillography after exercise. The prefix ton- was added to denote the supposed function of measuring blood pressure. It has been retained by the present authors to identify the method.

The inverse reaction found in patients with intermittent claudication may be an accentuation of a normal response to exercise. We have found that after exercising normal healthy young adults to points of extreme leg exhaustion, by making them run " on the spot " at full speed for as long as they can, an " inverse reaction " at the ankle may be demonstrated. This very severe degree of exercise was far in excess of exercise necessary to produce an inverse reaction in the claudication group. Fig. 8 shows an inverse reaction produced in a healthy young subject after very severe exercise.

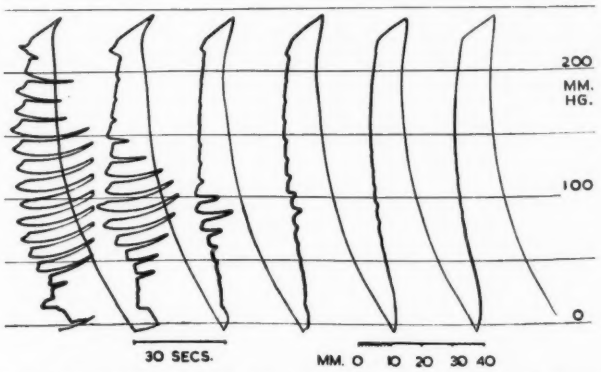

FIG. 7.—Tonoscillogram from right ankle of normal subject. The magnitude of pulsations has been decreased progressively in each tracing from left to right, by altering the amplification control on the apparatus. The difficulty in attempting to measure blood pressure from tonoscillograms is apparent from these tracings (see text). The subject's blood pressure in the right leg was, by the auscultatory method, 145/95.

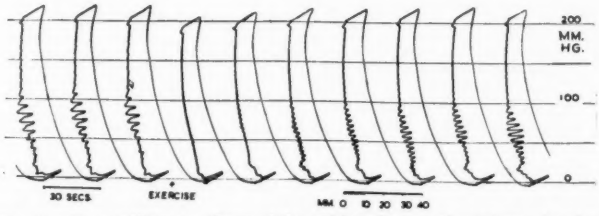

FIG. 8.—Tonoscillogram from right ankle of normal subject, showing " inverse reaction " produced after very severe exercise (see text).

A normal reaction was produced in the same subject after the most strenuous grade of exercise given to the intermittent claudication group, and it should be emphasized that in no control subject was an inverse reaction produced by the maximum degree of exercise required to produce it in any patient with intermittent claudication. The decrease in the magnitude of pulsations which some normal subjects show in the first tracing after much less exercise, further supports the possibility that the inverse reaction found in patients with intermittent claudication may be an accentuation of a normal response to exercise. All our arteriographed cases in Group 3 showed arterial obstruction and we have found no record of a proven case of intermittent claudication due to arterial spasm in the absence of obliterative arterial disease. Further work is being done with the object of determining the mechanism of the inverse reaction.

Summary

An exercise test, which may be performed either clinically or using Ejrup's tonoscillograph, is described and its use in the diagnosis of intermittent claudication is discussed. Forty-two normal subjects, four patients with pain in the legs not due to obliterative arterial disease, and fifty-three patients with intermittent claudication due to obliterative arterial disease have been studied by this method. In twenty-seven of the last group the diagnosis was confirmed by either arteriography or aortography. Pulsations in limb vessels after moderate exercise are found to increase or remain the same in normal subjects, and to decrease in those with intermittent claudication (the inverse reaction). The value of the finding of the inverse reaction in patients with intermittent claudication is discussed.

It is a pleasure to acknowledge the help and encouragement that we have received from Professor A. Kekwick in this work, and for his advice and that of Dr. John Goodwin in the preparation of the paper. We wish to thank members of the Consultant Staff of the Middlesex Hospital and others who have referred cases to us, Dr. David Sutton of the X-ray Diagnosis Department who performed the femoral arteriograms, also the secretaries, hospital photographer and hospital artist for their valuable assistance, and all those who acted as control subjects. We are indebted to the Board of Governors of the Middlesex Hospital who defrayed part of the cost of this investigation, and finally to Dr. Borje Ejrup of Stockholm for his very kind co-operation at all times.

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THE ROLE OF THE NERVOUS SYSTEM IN THE MAINTENANCE OF VENOUS HYPERTENSION IN HEART FAILURE

BY

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The mechanism of venous pressure elevation in chronic congestive heart failure is not yet well understood. Data collected in the last decade failed to substantiate the " backward failure " theory of high venous pressure. It was demonstrated that "high output failure" results in phlebohypertension as well as the " low output " form of the disease (McMichael, 1948). On the other hand, no increment in venous pressure occurs following severe damage (Starr *et al.*, 1943; Bakos, 1950) or temporary exclusion (Rodbard and Wagner, 1949) of the right ventricle, or after elevating venous resistance (Guyton, 1950) in the dog.

According to the " forward failure " theory (Warren and Stead, 1944), venous hypertension is caused by an increase in circulating blood volume in consequence of defective renal excretion of sodium. Venous pressure elevation produced by raising blood volume with enormous amounts of infusion fluids in dogs proved, however, to be only transient (Yeomans *et al.*, 1943; Gowdey *et al.*, 1950; Huckabee *et al.*, 1950). The high blood volume in erythræmia, and the sodium retention in chronic nephritis does not lead to venous hypertension (Landis *et al.*, 1946). The accumulation of œdema fluid does not always precede venous hypertension (Gibbons, 1948). High blood volume, as recently stated by Ross *et al.* (1950) does not seem to be a constant symptom of chronic heart failure.

The chief limitations of these hypotheses consist in the rigidly mechanistic view in which they explain the process of venous pressure elevation. Chronic congestive heart failure is the result of an inbalance between an increased demand (Hamburger and Lev, 1925) and a decreased supply of oxygen. In response to the resulting hypoxia, adaptive changes occur in tissue metabolism (Shorr *et al.*, 1951), in the adrenal cortex (Halmágyi *et al.*, in press), and in the circulation, the latter being mainly governed by the nervous system. Nervous regulation of hypoxia-induced circulatory changes is in good accord with the well known vulnerability of the brain towards lack of oxygen. The nervous system also influences the *veins* (reviewed by Gollwitzer-Meyer, 1932; and McDowall, 1935). The close correlation between changes of arteriolar and venous tone bespeaks a simultaneous spread of vasomotor impulses to arterioles and veins. In heart failure, however, an *independent* elevation of venous pressure occurs. Investigating the contribution of the venomotor tone in maintaining venous hypertension, two questions arose (Landis and Hortenstine, 1950):

Does the general contraction of the veins elevate their pressure?

Do the veins react as an independent part of the vascular system?

Most authors answer these questions in the negative (Landis and Hortenstine, 1950; Fremont-Smith, 1949; and others). Nevertheless, some isolated observations seemed to support these assumptions. Scaffidi *et al.* (1940), Delius *et al.* (1948), and Hammerschmidt *et al.* (1950) report a rise in venous pressure following administration of ergotamine derivatives. Paredrinol raises venous pressure by effecting a constriction of the veins (Iglauer *et al.*, 1940). Injection of tetra-

ethylammonium-bromide (TEAB) is followed by a sharp decline in previously elevated venous pressure (Hayward, 1948; Relman *et al.*, 1949; Schuman, 1950). Methonium compounds have a similar effect, as reported by Turner (1950). Sodium nitrite results in dilatation of the venules, as evidenced by Weiss *et al.* (1937) and Willkins *et al.* (1937, 1938). All these data refer to peripheral venous pressure, without simultaneously determining other circulatory factors.

The following experiments represent an attempt to re-evaluate and extend the available data with the aid of modern clinical methods not being in use at the time of earlier studies.

Methods and Material

Investigations were carried out on 84 men and women, in the early morning hours, at least eight hours after the intake of the last meal. Sixty-two of them suffered from chronic congestive heart failure of various origin. None of them received any treatment or sedative prior to the experiments.

In about half of the cases cardiac catheterization was performed, as described by Cournand and Ranges (1941). The tip of the catheter was placed in the right atrium under X-ray control, through a needle inserted in the antecubital vein. A permanent cannula was inserted in the femoral artery too. Pain was prevented by novocaine anæsthesia. Oxygen consumption was measured by using a standard basal-metabolism equipment (system Knipping); arterial and venous blood samples were simultaneously withdrawn. The patient was placed during the whole procedure on a specially fitted X-ray table, providing relative comfort. Observations were started 30 minutes following the insertion of the catheter and the arterial cannula, at a time when pulse rate and pressures were stabilized on a resting level.

The determination of cardiac output was based on the Fick principle, and was calculated on one square meter body surface area (cardiac index). Arterio-venous oxygen difference was determined photoelectrically (Issekutz *et al.*, 1949).

Right atrial and femoral arterial pressures were measured with a Sanborn electromanometer (Rappaport and Sarnoff, 1949) which recorded on an Elmquist cardiograph. Mean pressures were obtained by electric integration. Peripheral venous pressure was measured with a saline manometer in the antecubital vein. The zero point for all measurements was 10 cm. anterior to the back, with the patient recumbent.

If not stated otherwise, substances were administered by a slow intracardiac or intravenous infusion by means of an electric pressure pump. Prior to and following all procedures, cardiac output and pressures were repeatedly determined. Each individual value represented the average of at least two separate determinations, not deviating more than 5 per cent.

Dihydroergotamine (DHE—Sandoz), 1 mg.; hydergin (Sandoz), a mixture of DH-ergokryptine, DH-ergocornine, and DH-ergokrystine, 0·3 mg.; and sodium nitrite, 0·04–0·06 g. were administered to study the influence of substances effecting the smooth muscle of the vascular system. Pulsoton (chinoin) (m.-oxyphenyl-isopropyl-amine), 0·005–0·01 g. was given investigating the effect of a sympathomimetic agent on venous pressure.

TEAB (4–6 mg./kg. body weight), atropine sulphate (Merck, 1 mg.), and N,N-dibenzyl-β-chloroæthylamine-HCl (dibenamine, 3–5 mg./kg. body weight) were given to establish the effect of ganglionic, sympathetic, and parasympathetic blocking on venous pressure. The dibenamine infusion lasted 40–50 minutes, and was preceded by barbiturate sedation to avoid untoward central excitation (Nickerson and Goodman, 1948).

The role of the central nervous system in maintaining venous hypertension was studied during sleep. Sleep was induced by administering sodium amytal (0·20–0·40 g.), orally; in other cases evipan sodium (0·50–0·75 g.), intramuscularly; or chloralhydrate (1·5 g.), rectally. In one instance the patient spontaneously fell asleep. Criteria of optimal sleep were as follows: (*a*) the absence of initial excitation, (*b*) quietness and depth of sleep, (*c*) normal respiration, (*d*) the possibility of waking the patient at any time with any simple stimulus. Experiments not conforming to these

requirements were disregarded. In three cases administration of 0·75 g. evipan sodium failed to induce sleep. In a single case 0·50 g. evipan sodium was followed by deep coma necessitating the administration of picrotoxine. These cases served as control observations regarding the effect of insufficient or toxic doses of barbiturate.

Another series of experiments were carried out on male and female, unanæsthetized animals: 7 dogs (8–15 kg.), and 4 cats (2–3 kg.). Arterial pressure was measured in the right femoral artery using a mercury manometer, and venous pressure was measured in the left femoral vein by means of a saline manometer. Reference level was a point 5 cm. above the surface of the table. The animals received intravenously 0·1–1·0 mg./kg. body weight of ergotamine (gynergen—Sandoz), or DHE. Four dogs were subjected to intravenous saline infusions. The priming rate of the infusion was 17 ml./min. kg. body weight. This was followed by a sustaining rate of 1–3 ml./min./kg. body weight. Pressures were continuously determined. At the maximum level of the venous pressure increase TEAB was given in a dose of 5–10 mg./kg. body weight, intravenously.

Owing to the many groups of individual experiments, a form of tabulation was devised promising an easy survey of the results. The figures of Table I represent mean values of the individual experiments. The statistical significance of the differences was calculated by the " table of ' t ' " (Fisher, 1934).

Results

Effect of Ergotamine Derivatives. Circulatory changes following the administration of DHE are shown in Group I of Table I. A significant increase in peripheral and central venous pressure occurred. No significant change was observed in arterial pressure and cardiac output. The rise in venous pressure preceded the onset of bradycardia (Fig. 1). Simultaneous pressure measurement in the antecubital vein and right atrium following DHE administration indicated an increase in the venous pressure gradient (Fig. 2). The venous pressure elevation lasted several hours. No difference could be demonstrated in the effect of DHE on normal persons and on patients in heart failure.

The effect of previously administered atropine on venous pressure elevation following DHE

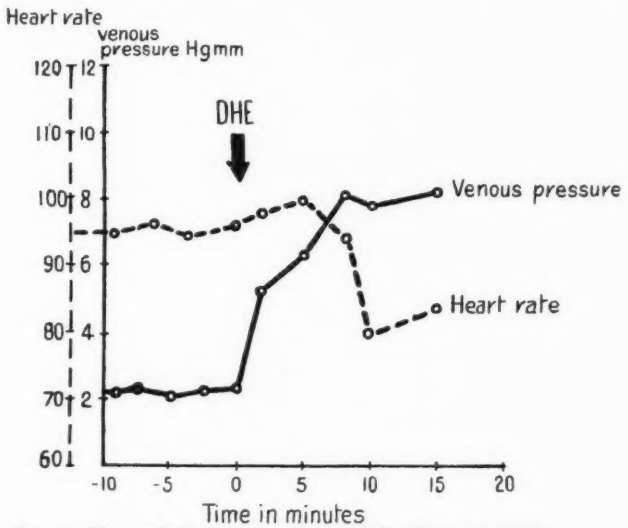

FIG. 1.—Time relation of two characteristic effects of DHE: venous hypertension and bradycardia.

TABLE I

THE EFFECT OF VARIOUS DRUGS AND INTERVENTIONS ON ARTERIAL, RIGHT ATRIAL, AND PERIPHERAL VENOUS PRESSURE, AND CARDIAC OUTPUT IN CHRONIC CONGESTIVE HEART FAILURE

No. of Groups	Intervention	No. of Experiments	Mean of Arterial Systolic Pressures in Hg mm.				Mean of Venous or Right Atrial Pressures in Hg mm.				Mean of Cardiac Indices (l./min.) (cardiac output per sq. m. body surface area)			
			Before Intervention	After Intervention	Difference	Significance of difference	Before Intervention	After Intervention	Difference	Significance of difference	Before Intervention	After Intervention	Difference	Significance of difference
I	Dihydroergotamine (1 mg. i.v.)	28	123	125	+2	None	8·3	15·0	+6·7 (+81%)	t=9·70 p<0·01	4·11	4·22	+0·11	None
II	Hydergin (0·3 mg. i.v.)	6	146	134	−12	t=6·94 p<0·01	9·7	11·2	+1·5 (+17%)	t=1·68 p>0·01	—	—	—	—
III	Sodium nitrite (40–60 mg. i.v.)	14	132	127	−5	None	12·3	8·0	−4·3 (−35%)	t=6·85 p<0·10)	3·02	3·66	+9·64	t=4·30 p=0·01
IV	Tetraethylammonium (200–300 mg. i.v.)	11	168	117	−51	t=4·97 p<0·01	20·1	13·4	−6·7 (−33%)	t=8·60 p<0·01	3·46	4·72	+1·26	t=1·29 p>0·20
V	Dibenamine (120–240 mg. i.v.)	9	168	154	−14	None	11·8	7·5	−4·3 (−36%)	t=3·59 p<0·01	2·55	2·56	+0·01	None
VI	Sleep	11	137	122	−15	t=5·25 p<0·01	13·8	8·6	−5·2 (−38%)	t=4·73 p<0·01	2·77	2·99	+0·22	None
VII	Evipan sodium (500–750 mg. i.m.)	3	130	120	−10	—	13·7	14·2	+0·5	—	3·91	4·07	+0·16	—
VIII	Barbiturate (coma)	1	160	100	−60	—	12·6	18·2	+5·6	—	3·17	2·48	−0·69	—

Significances of differences were estimated with Fisher's " t " test (Fisher: " *Statistical Methods for Research Workers*," London, 1934, Oliver and Boyd.

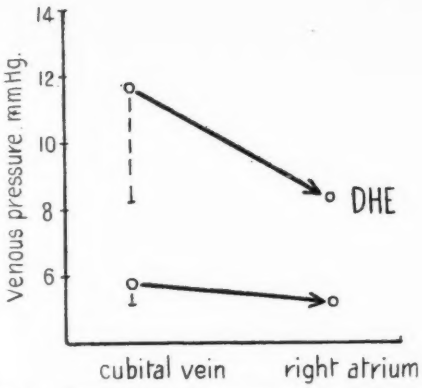

FIG. 2.—Change in the venous pressure gradient following administration of DHE.

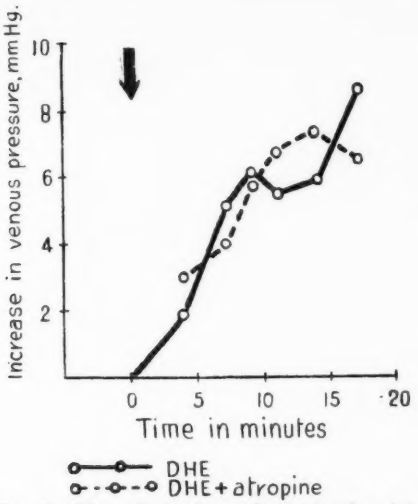

FIG. 3.—The effect of previous atropine intake on DHE induced venous hypertension.

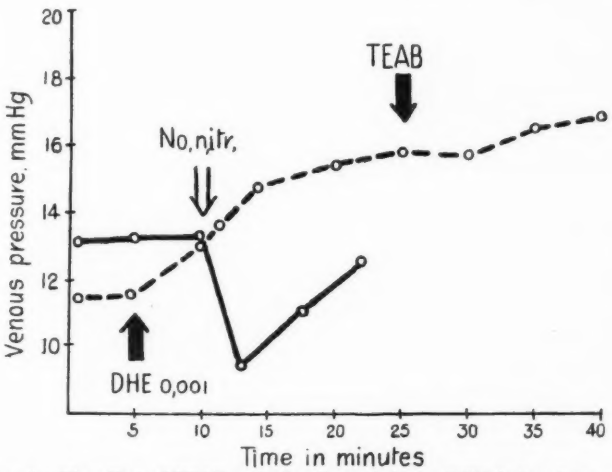

FIG. 4.—The effect of TEAB and of sodium nitrite on DHE induced venous hypertension.

intake was studied. The effect of DHE on venous pressure was established on six normal and cardiac patients. The next day the experiment was repeated after having previously administered atropine. The onset of the effect of atropine was controlled on the pulse rate and pupils. Fig. 3 illustrates the average values. Atropine does not seem to influence the effect of DHE on venous pressure, nor does it influence venous hypertension when administered following DHE intake.

Venous pressure elevation brought about by DHE was not influenced by TEAB, but dropped promptly to almost normal levels after administration of sodium nitrite (Fig. 4).

Hydergin resulted in a less pronounced increase of venous pressure (Group II of Table I).

Ergotamine and DHE did not influence the venous pressure in three dogs and four cats.

Pulsoton was given to three persons and pressures on the venous and arterial sides of the circulation were registered. Pressure increased on both sides. Administration of DHE resulted in a further increase in venous pressure, arterial pressure remaining unaltered (Fig. 5).

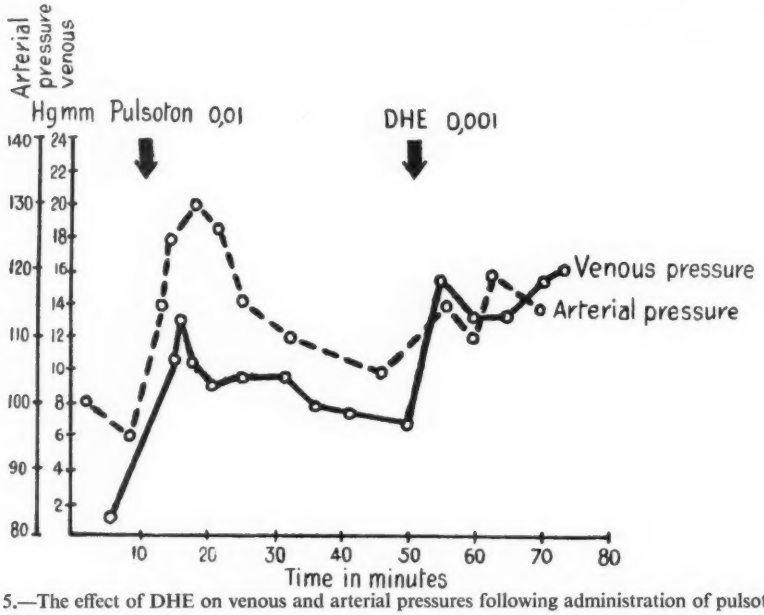

FIG. 5.—The effect of DHE on venous and arterial pressures following administration of pulsoton.

Effect of Sodium Nitrite. Circulatory changes following administration of sodium nitrite in congestive heart failure are demonstrated in Group III of Table I. A marked decrease in right atrial pressure and an increase in cardiac output occurred. Arterial pressure remained practically unchanged. Calculating the correlation between the changes in venous pressure and cardiac output, the most probable regression coefficient was found to be 12·0, with a standard error of 17·1. A causal connection between increase in cardiac output and in decrease in right atrial pressure seems therefore unlikely. Sodium nitrite had no effect on normal venous pressure.

Effect of TEAB. Circulatory changes following the administration of TEAB in congestive heart failure are demonstrated in Group IV of Table I. TEAB resulted in a marked drop in right atrial and arterial pressures, with a simultaneous (but hardly significant) increase in cardiac output. No effect was observed on normal venous pressure.

The elevated venous pressure in dogs subjected to large, rapid, intravenous infusion, remained unaltered following administration of TEAB (Fig. 6).

Effect of Dibenamine. Circulatory changes following administration of dibenamine in congestive heart failure are demonstrated in Group V of Table I. Dibenamine resulted in a marked decrease of right atrial pressure. Cardiac output remained unaltered. The decrease of venous pressure preceded all other well known effects of the drug, as arterial hypotension, mydriasis, and coryza (Fig. 7). These were only observed some hours after the experiment had been completed. No effect was observed on normal venous pressure.

Effect of Sleep. Hæmodynamics of sleep in congestive heart failure are demonstrated in Group VI of Table I. Besides a decrease in arterial pressure a marked decrease in right atrial

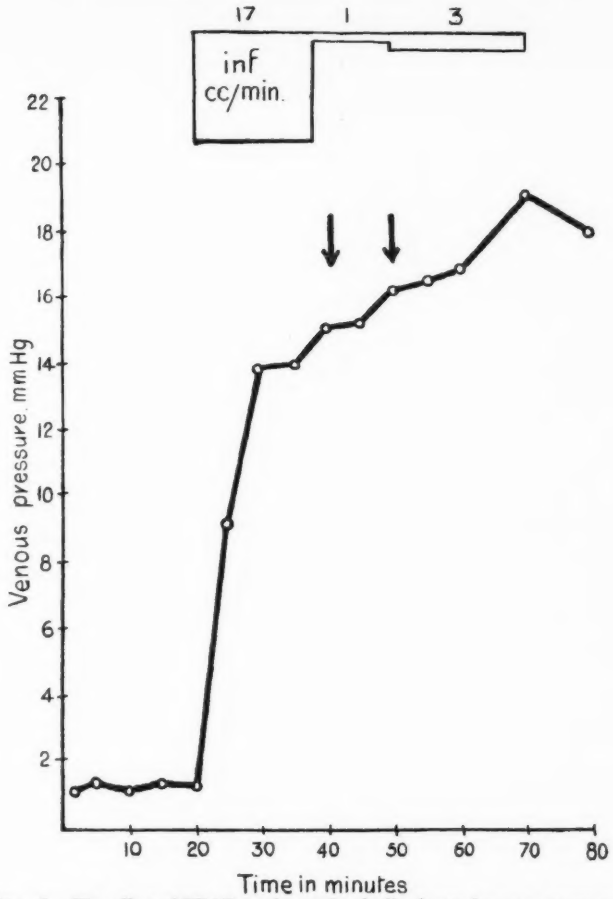

FIG. 6.—The effect of TEAB on the mechanically elevated venous pressure of the dog. The arrows represent the intravenous administration of 5·5 mg./kg. body weight of TEAB.

pressure occurred. Cardiac output increased slightly. After waking the patient venous pressure rapidly returned to starting levels (Fig. 8). In cases where administration of evipan failed to induce sleep no significant changes occurred (Group VII of Table I).

A toxic dose of evipan resulted in a further *elevation* of right auricular pressure and in a decrease in cardiac output and arterial pressure. The changes in right auricular pressure and cardiac output are opposite to those observed during sleep (Group VIII of Table I).

Sleep has no effect on normal venous pressure.

DISCUSSION

Besides their sympathicolytic property, ergotamine derivatives possess a vasoconstrictor effect due to their direct action on vascular smooth muscle. Delius *et al.* (1948) and Hammerschmidt *et al.* (1950) attributed the rise in venous pressure following their intake to this effect. This view was

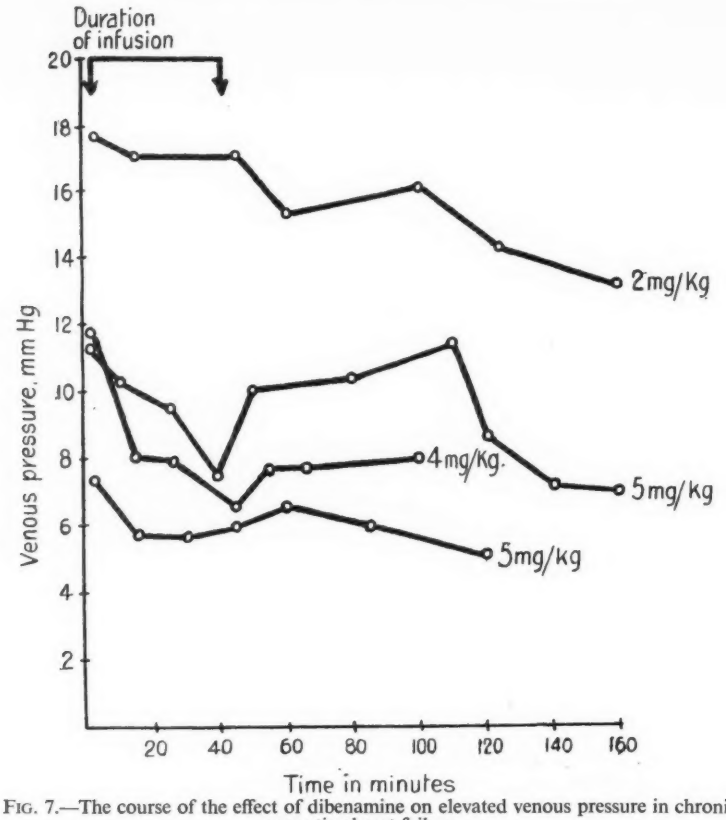

FIG. 7.—The course of the effect of dibenamine on elevated venous pressure in chronic congestive heart failure.

supported by the following observations. Venous hypertension resulting from DHE administration: (*a*) is brought about without significant changes in arterio-venous oxygen difference or cardiac output, (*b*) is neither prevented nor discontinued by TEAB (Fig. 4), nor atropine (Fig. 3), (*c*) is completely reversed by sodium nitrite (Fig. 4), (*d*) is less marked following hydergin (Group II of Table I), and (*e*) ensues before the onset of bradycardia (Fig. 1).

Supposing that the effect of DHE in elevating venous pressure is unrelated to its sympatholytic activity and is caused by vasoconstriction, the *seat* of this vasoconstriction had to be decided. It is unlikely to be located on the *arterial* side of the circulation. *Venous* constriction, as a cause of venous hypertension is, however, not unanimously accepted. Landis and Hortenstine (1950) suggest that widespread venous constriction raises central venous pressure only if the heart can not accept the added venous return because it is unable through reduced competence to elevate its output correspondingly. This assumption was not supported: pressure elevation following DHE administration was similar both in normal and in decompensated patients. Fremont-Smith (1949) points out that constriction of the veins increase their *resistance* and not their *pressure*. DHE does not influence venous pressure in animals, despite the similarity of action in all other respects. It seems that the effect of venous constriction on venous pressure is different in man and in animals. This assumption may be supported by the fact that venous hypertension of endogenous origin (chronic congestive heart failure) is an extremely rare condition in animals.

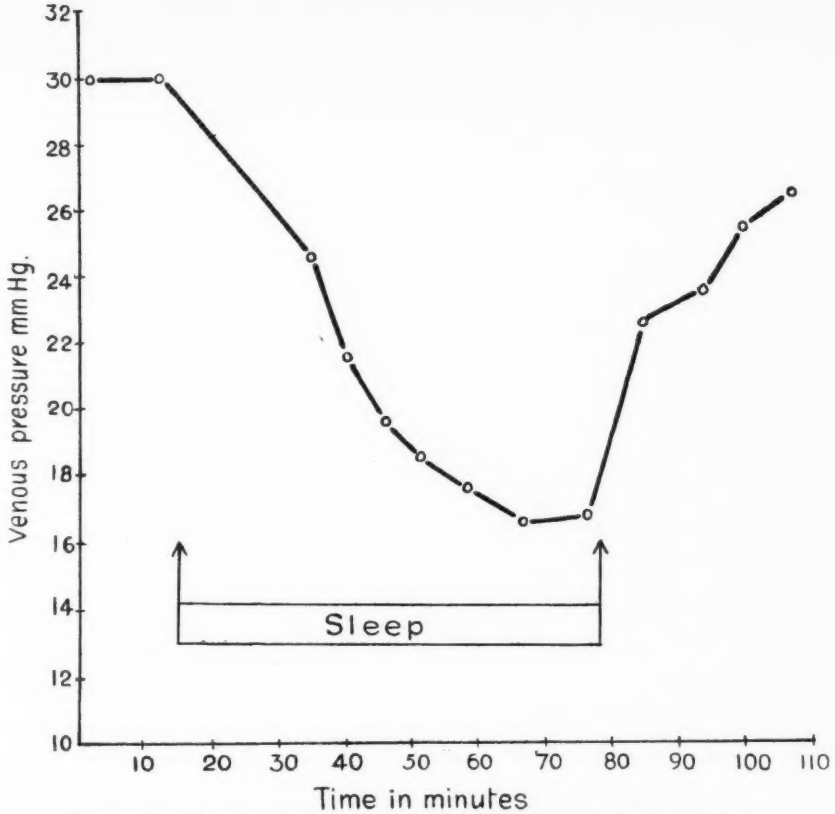

FIG. 8.—The effect of sleep on venous pressure in chronic congestive heart failure.

By accepting the venous pressure raising effect of venous constriction, a new contradiction emerges. In congestive heart failure there is a marked *dilatation* of the visible veins. Stead (1949) assumes that the dilatation concerns only the large, visible veins, with a simultaneous constriction of the small ones. This view seems to be supported by the effect of sodium nitrite (Group III of Table I), causing venous dilatation as a result of relaxation of smooth muscle. It seems that in the absence of venous constriction sodium nitrite would be unable to reduce venous pressure in congestive heart failure: normal venous pressure remains uninfluenced.

It is characteristic of both substances that they influence venous pressure in a dose insufficient to alter arterial pressure.

The effect of drugs acting on different parts of the nervous system led to the conclusion that this presumable venous constriction is under nervous control.

The decrease of right atrial pressure in heart failure following administration of TEAB (Group IV of Table I) is incident to a simultaneous decrease in arterial pressure and increase in cardiac output. The decrease of right atrial pressure is, however, not a mere consequence of the latter two changes. This seems to be proven by the following observations: right atrial pressure decreased even in those cases where no increase in cardiac output occurred; the venous pressure of dogs subjected to large intravenous infusions, did not decrease following injection of TEAB, despite its similar effect on arterial pressure and cardiac output (Fig. 6). This latter observation seems

further to indicate that a simple elevation of circulating plasma volume does not create a condition similar to human congestive heart failure: whereas the former is a simple mechanical distension of the venous system, the latter is a true venous hypertension, being—in analogy to benign arterial hypertension—due to an active participation of the nervous system. (The possibility of a nervously mediated independent venous hypertension was at first emphasized by Condorelli, 1947.) A further support of the above statement is found in the effect of dibenamine, and in that of sleep. Dibenamine resulted in a decrease in venous pressure in congestive heart failure (Group V of Table I.) This decrease, however, was in most cases unrelated to the effect on the arterial pressure, and occurred without any concomitant change in cardiac output. No explanation is offered for the early occurrence (Fig. 7) of this effect.

The analogous mechanism of arterial and venous hypertension is further supported by observations made during sleep (Group VI of Table I). It has long been known that arterial pressure of hypertensive subjects decreases during sleep, showing the role of the central nervous system in the maintenance of benign arterial hypertension. Venous pressure in congestive heart failure exhibits a similar reversible decrease during sleep (Fig. 8), appearing to be unrelated to a simultaneous change in arterial pressure and cardiac output.

Frew and Rosenheim (1949) in their paper on the labile neurogenic component of arterial hypertension emphasize the existence of a common neurogenic element (" supplemental pressure," Alam and Smirk, 1943). They proved that TEAB and barbiturate act upon the same neurogenic element of hypertension though at different levels of the reflex arc: the minimum diastolic pressures obtained with TEAB and barbiturates in cases of arterial hypertension were identical. The venous pressure in heart failure behaves in a similar manner. By blocking muscular or neurogenic impulses with sodium nitrite, TEAB, dibenamine, or sleep, the decrease in venous pressure is always the same: about 35 per cent (Table I). It seems that mechanical factors are only responsible for the rest of the venous hypertension. Yet a difference from arterial hypertension exists. While the removal of the neurogenic element may have little effect in advanced stages of arterial hypertension, the neurogenic element of venous hypertension seems to bear no relation to the time of onset or progress of heart failure.

The above experiments fail to throw light on the unknown stimulus causing the nervous excitation which leads to venous hypertension. Anoxia alone does not seem to be responsible for this phenomenon: cyanotic forms of congenital heart disease fail to exhibit elevated venous pressure.

Patients were not especially benefited by the decrease in venous pressure, brought about by the administration of the aforementioned, extracardially acting substances; diuresis was never enhanced. This observation seems to support the view that despite predominance of peripheral signs, the final cause of the complex clinical entity, known as chronic congestive heart failure is, after all, the failing myocardium (Ahmed *et al.*, 1950).

In face of the facts pointing out the important part of the nervous system in maintaining venous hypertension, Pavlov's words may be recalled (1951): " . . . The more the nervous system of an organism is developed, the more its highest section predominates in organizing and arranging all its bodily functions, although this is not always manifest."

A study concerning the role of the nervous system in maintenance of pulmonary hypertension is in progress.

SUMMARY

In an attempt to investigate the possibility of independent reactions of the venous system, the following facts were established. Ergotamine derivations cause a rise in peripheral and central venous pressure in man, but not in animals. Sodium nitrite decreases the right atrial pressure in heart failure, but not in normal persons. Both drugs exert their action by affecting the smooth muscle of the veins. Contraction or relaxation of the muscle of the venous system seems to result in a rise or decrease in its pressure. Phlebohypertension in heart failure is partly due to a constriction of the small veins.

Venous constriction in heart failure is mediated by the sympathetic nervous system and controlled by higher brain centres. In analogy with benign arterial hypertension, venous hypertension also possesses a " common neurogenic component " (Frew and Rosenheim, 1949). Venous pressure elevation in dogs subjected to a large intravenous infusions does not decrease following administration of TEAB. The conclusion was reached that expanding blood volume does not create conditions identical with human heart failure.

High venous pressure in heart failure is a combination of two factors: (*a*) a mechanical factor (high blood volume, back pressure, etc.), and (*b*) a functional factor (nervously produced venous constriction).

Our thanks are due to Mr. K. Szeitz for his invaluable help and assistance.

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CLINICAL ELECTROCARDIOGRAPHY: THREE-DIMENSIONAL VISUAL AIDS TO TEACHING

BY

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Empiric interpretation of the clinical electrocardiogram is no longer adequate. The fundamental contributions of Wilson and Goldberger have led to the common clinical use of 12 leads—three standard, three augmented extremity, and six præcordial. If the interpreter is to gain the most knowledge from the information available in these leads, an understanding of the electrical position of the heart in each instance is essential.

Visual aids to the teaching of any spatial principle are of obvious value. Goldberger's book (1949) applies two-dimensional illustrations to the relation of cardiac position and fixed unipolar electrocardiographic leads within the electrical field. This article describes two three-dimensional diagrammatic models of the ventricular heart related to the common fixed leads. One is more applicable to the seminar or individual discussion, the other to the classroom.

DESCRIPTION

One aid * (Fig. 1) consists of a model roughly fashioned to resemble the ventricles sectioned from the total heart just below the valvular level. Size and shape are those of small normal ventricles. The left ventricular portion with septal wall is carved in soft wood from which a small ventricular cavity is hollowed out. The right ventricular portion is of 1/8 inch transparent plastic, moulded to complete the semi-spherical ventricular structure. For further clarity the left ventricle is painted red, and the septal wall facing the cavity of the right ventricle white. This model is hung at the center of a 10-inch circle of 1/4-inch round steel mounted on a wooden base. The model is joined to its suspending bar by a swivel. The swivel permits the ventricular model to rotate through 360°, to swing in any plane through an arc of 180°, and to remain in whatever position fixed by friction joint. Relative field positions of arm leads and left leg lead are marked on the metal circle by welded tabs labelled R, L, and F. A bar of 1/4 by 3/8-inch plastic is formed into a shallow arc and fastened in horizontal plane to the metal circle from a 9 to 3 o'clock position. Relative field positions of chest leads 1, 2, and 5 are stamped on the plastic. A sliding tab rides the plastic arc to mark any labelled or interpolated position under consideration.

By means of this three-dimensional diagram the ventricular model can be fixed in any position in its electrical field relative to the fixed positions of three limb and antêro-lateral chest leads. The electrical source of positive and negative components of the QRS complex as " seen " from any single relatively unipolar lead can be readily visualized. The user must, of course, project from his imagination any alteration of ventricular size or contour attributable to hypertrophy or disease.

The second aid (Fig. 2) † is somewhat similarly conceived, but differently executed. Here

* Made for one of us (T.J.R.) by Mr. Gil Bartlett, Wichita, Kansas, at a cost of $25.00 for labour and material.
† Made by one of us (E.G.D.), cost of plastic $8.00.

the positions of leads are represented on two large bisecting planes of 1/4-inch transparent plastic in vertical and horizontal positions. The vertical plane is triangular and measures 18 inches on each side. The horizontal plane is a circle 18 inches in diameter. The triangle rests in and can be removed from the circle which is supported on a wooden tripod. The center of the bisection of the plastic planes is cut out to accommodate a hollow hemisphere made from half a rubber ball. This represents the ventricles and is painted one half blue and one half red to indicate the right and left ventricle. A separate plastic " card " is shaped to fit loosely within the ball to represent the

FIG. 1.—Ventricle and ring model. See text and subsequent figures for application.

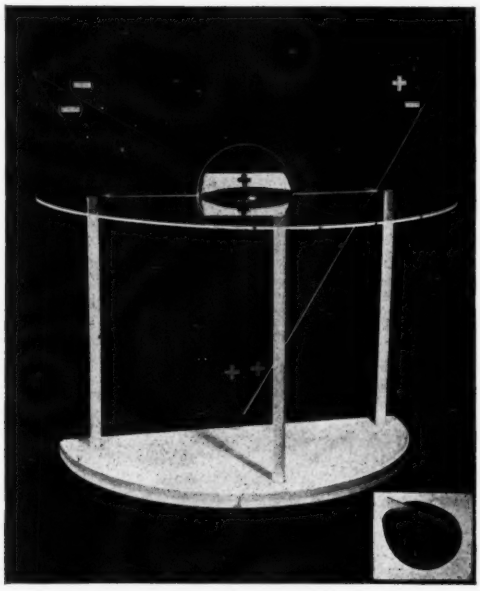

FIG. 2.—Plastic plane model. See text for application.

ventricular septum. This is painted black on one side and white on the other to indicate negativity and positivity. The " septum " within the ventricles and the " ventricles " within the bisecting planes can be placed in any position dictated by the circumstances of demonstration or the pattern of electrocardiographic tracings. Positions of chest leads 1 to 6 are indicated by radiating lines drawn on the horizontal plane. The corners of the triangle represent the limb leads and are marked with positive and negative symbols. These symbols with lines bisecting the triangle from each corner serve to illustrate the principles of Einthoven's triangle when this plane is lifted from the supporting horizontal one.

USE AND EXAMPLES

Excepting as they can be shown to be combinations of lead potentials the standard leads I, II, and III are not used in model positioning. Fig. 3 and 4 show the first model with the ventricles in vertical and horizontal positions, with appropriate electrocardiograms.

In the vertical heart the position is achieved in the following manner. Lead aVR shows a QS or Qr pattern typical of a lead facing the ventricular cavity, so also does lead aVL. Therefore

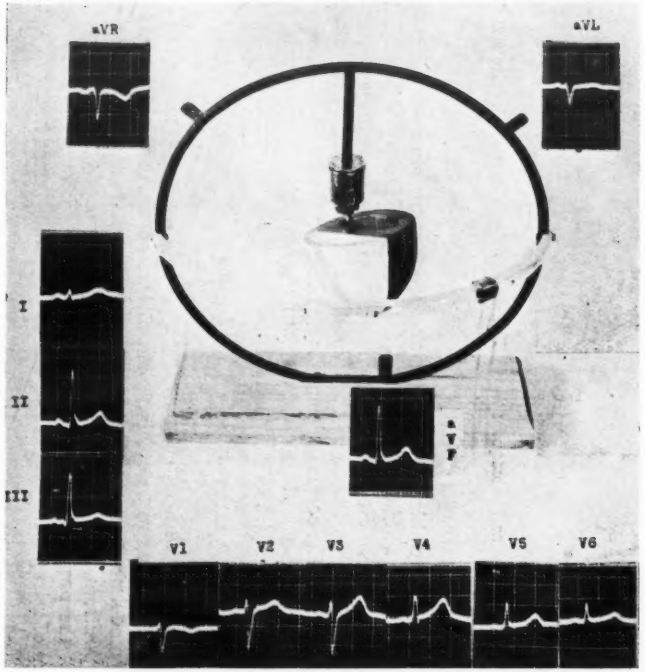

FIG. 3.—Normal vertical heart. aVR and aVL show a QS pattern from the cavity of the heart. aVF shows a qR pattern from the epicardial surface of the left ventricle. Præcordial leads show a normal position of rotation upon the long vertical axis.

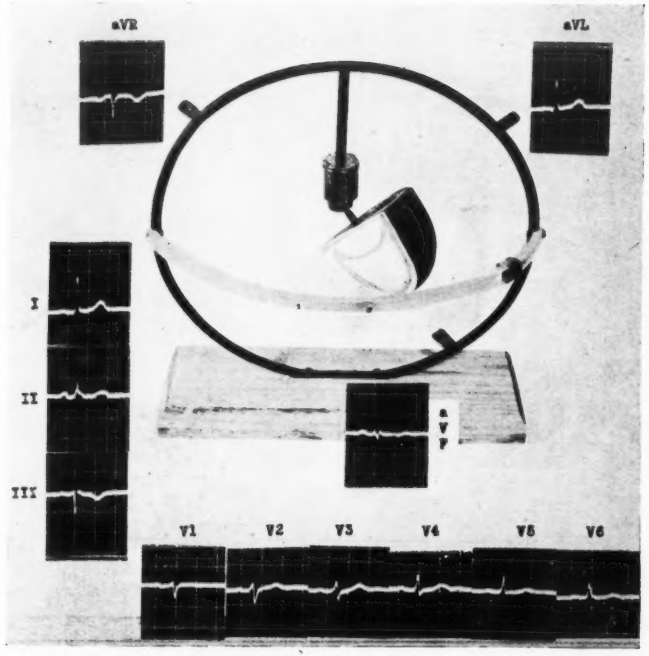

FIG. 4.—Normal horizontal heart. aVR shows a QS pattern from the cavity of the heart. aVL shows a qR pattern from the epicardial surface of the left ventricle. aVF shows a rSr′ from the apical portion of the right ventricle. Præcordial leads show a normal position of rotation upon the long verticle axis.

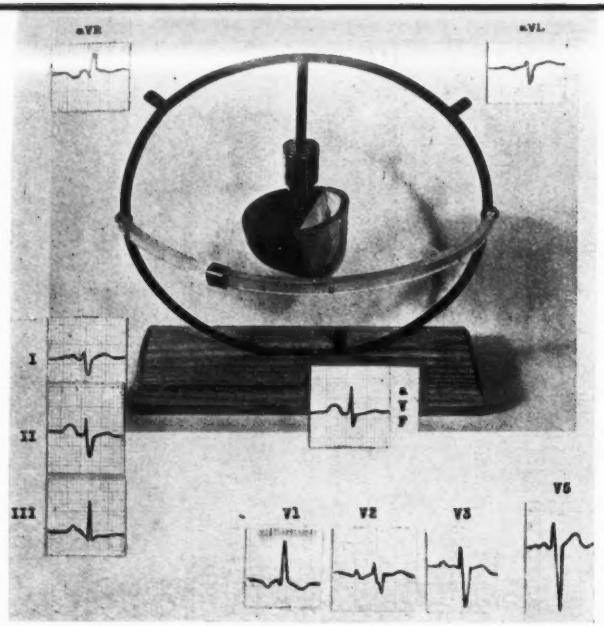

FIG. 5.—(Tracings retouched for photography.) Mitral stenosis. The heart is vertical and rotated clockwise 180°. Ventricular complex in lead V1 shows qR from the epicardial surface of the left ventricle. Ventricular complex aVR shows qR pattern also of the left ventricle. Ventricular complex aVL resembles that normally seen in aVR. Note broadened and deformed P waves. (The right ventricle must be visualized as constituting a greater portion of ventricular volume than is shown in the model.)

(Male, aged 33. B.P. 130/90. Systolic and presystolic murmurs of mitral stenosis. X-ray configuration of mitral stenosis with pulmonary congestion. After initial relief of failure, patient again became febrile, developed hepatitis and an enlarged spleen and died.

Necropsy showed a very limited slit of mitral stenosis with old verrucal valvulitis; left atrial dilatation and right ventricle hypertrophy, and confirmed position of heart essentially as shown in model. Tissue section showed generalized changes of diffuse collagen disease suggestive of lupus, though " wire loop " lesions of kidney not present.)

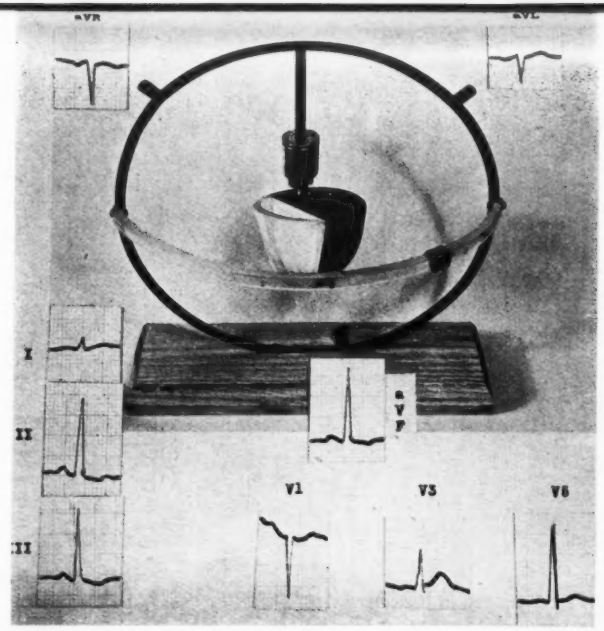

FIG. 6.—(Tracings retouched for photography.) Hypertensive heart disease. The heart is vertical. Ventricular complex in aVF shows high R and depression of S–T to low inversion of T. These characteristics are repeated in standard leads II and III.

(Male, aged 26. Known hypertension six years. Admitted because of first anginal pain with subsequent milder discomfort for two weeks. B.P. 200/110. Spasm of retinal arteries. A2 loud. Cardiac fluoroscopy showed only slight ventricular prominence posteriorly.)

the model is positioned with the ventricular cavity up. This vertical position is confirmed by and further drawn from a qR, qRs, R or Rs pattern in lead aVF. The predominant R shows aVF alone among the limb leads to face the epicardial surface of the left ventricle.

In the horizontal heart aVF also shows a QS pattern. The beginning position of the model is also with the cavity of the ventricles up. Lead aVL, however, shows a qR pattern. The small initial q indicates the lead to be facing the negative or left side of the septum, the prominent R shows it to be facing the epicardial surface of the left ventricle. The model is tilted so that the lateral surface of the left ventricle faces the tab marked L. The horizontal position is confirmed and further drawn from an rSr pattern in lead aVF. The small r indicates the lead to be facing the positive or right side of the septum, the S that the summation of major potential is of the endocardial surface of the left ventricle " seen " through the right. Therefore, the apical surface of the right ventricle should be positioned to face the tab F.

In either instance, horizontal or vertical, the rotation of the heart upon its vertical axis can be determined by reference to the chest leads. In normal positions V1 should face the right ventricle and show an rS pattern, lead V6 should face the epicardial surface of the left ventricle and show a qR pattern. By consideration of the shift of pattern through V2–V5 the model can be placed in approximate clockwise or counterclockwise rotation upon its vertical axis.

These oversimplified normal positions are seen with reasonable frequency in clinical tracings and serve as reference points for the solution of less obvious cardiac positions.

Fig. 5 shows the cardiac position by model and the clinical tracing in a case of mitral stenosis. Clockwise rotation is so extreme that lead V1 shows a qR pattern from the epicardial surface of the left ventricle.

One of the most pertinent clinical demonstrations of the model is seen in left heart " strain " in the vertical heart (Fig. 6). Here the abnormal S–TT segment change is seen in aVF where the septal q and prominent R indicate the epicardial surface of the left ventricle facing the diaphragm, with a vertical heart. The abnormality of lead aVF is reflected in standard leads II and III. Empiric interpretation of standard leads could lead to the inference of right heart " strain."

Further elaboration by example is beyond the purpose of this presentation. The authors have found the ring and ventricle model very useful in ward teaching by specific clinical application.

The large plastic model has been a useful visual aid particularly for beginning instruction with groups who have been familiar with the three standard leads but have difficulty in visualizing the relationship of the limb leads as a frontal plane section and the chest leads as a horizontal plane section. The triangle is lifted out of the model and held in front of the lecturer. When the group has assimilated this concept, the triangle is returned to the model and three-dimensional relationships are developed.

Conclusion

Two three-dimensional models of the cardiac ventricles in relation to limb and chest electrocardiographic leads are described. Their value to teaching is noted. Examples of their application are presented.

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ERRATUM

British Heart Journal, January, 1952

"Clinical Electrocardiography—Three-dimensional Visual Aids to Teaching," by T. J. Rankin and E. Grey Dimond.

P. 116 lines 2 and 4 'aVF' should read 'aVR'.

THE HEART IN HÆMOCHROMATOSIS

BY

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The purpose of this paper is to give a brief account of present-day knowledge of the effects of æmochromatosis upon the heart after which we shall describe two cases of the disease in which ardiac involvement was a prominent feature stimulating our interest in this subject. The involvement of the heart in hæmochromatosis is well known. Infiltration of hæmosiderin varies from edge-shaped deposits at the nuclear poles of the muscle fibres to the extreme degree in which the bres may be replaced by a mass of pigment granules contained within the muscle sheath. Hæmoderin may also be found in the connective tissue, lying free in the lymph spaces, or within fibroasts and mononuclear cells. An increase of fibrous tissue has been considered to be rare. æmofuscin is also found in the muscle fibres arranged in the same way as hæmosiderin (Sheldon, 935).

In his review of 311 cases of hæmochromatosis Sheldon states that myocardial failure is uncommon and he places it as the cause of death in a miscellaneous group (15 per cent of 119 cases in hich the cause of death was evident) which includes various intercurrent conditions. Within the ast seventeen years a number of reports have appeared of cases of hæmochromatosis in which cariac symptoms followed by death in congestive heart failure have occurred. We have selected ten eports comprising fourteen cases which are arranged in Table I. It is a pity that the pathological ata are often very meagre. Significant coronary sclerosis or valvular lesions were not described xcept in the case of Blumer and Nesbit (1938) in which there was a moderate degree of coronary theroma.

Cardiac enlargement was noted in eleven cases, in four on clinical grounds only and in the emainder on radiography or necropsy or both.

Electrocardiographic findings are given for twelve cases. Four were normal, one after having hown T wave changes. Three showed low voltage; seven showed T wave changes other than in ead III; there were three examples of auricular fibrillation and one of auricular flutter; there as one paroxysm of supraventricular tachycardia. There were two cases of complete heart block nd one of prolonged P–R interval.

Substernal pain is mentioned in five cases. In two it was severe and in one it was often related o exertion. In one case, pain over a period of three weeks occurred three years before his death n heart failure. Necropsy in two instances showed myocardial fibrosis but there was coronary isease in only one (Blumer and Nesbit, 1938) and it was not severe. No myocardial infarction was ound in any case.

Congestive heart failure closed the illness in all the fatal cases.

On the subject of the heart in hæmochromatosis, there have been a number of reports by rench authors who have striven to invoke an endocrine origin for the observed heart failure ithout satisfying the reader or, apparently, themselves. The clinical reports describe cases that re comparable with the present series and doubtless represent the same disease process (de Gennes *t al.*, 1936; Oumansky and Longuet, 1938).

TABLE I

SOME PREVIOUSLY REPORTED CASES OF HEART DISEASE AND FAILURE IN HÆMOCHROMATOSIS

No.	Author and Date	Age	Sex	Diabetes	Cardiac Symptoms and Signs	Electrocardiogram	Heart and Myocardium
1	Cann, 1933	56	M	Yes	None	T flat in all leads	Much scarring. Moderate fibrosis. Muscle fibres infiltrated with brown pigment granules.
2	Althausen and Kerr, 1933	59	M	Yes	Dyspnœa. Palpitation. Œdema. Enlarged left ventricle.	T II flat. T III inverted. Later auricular fibrillation.	"Diffuse sclerosis." No further details.
		43	M	Yes	Dyspnœa. Auricular fibrillation	"Essentially normal" after quinidine.	Alive, 1933.
		21	M	Yes	Systolic murmur. Enlarged left ventricle.	A-V block and auricular flutter	Died in congestive failure. No necropsy.
3	Darnall, 1935	41	M	No	Pain in abdomen and lower sternum. Details inadequate.	No definite abnormality	"Pigment deposition." No further details.
4	Murray Lyon, 1936	27	M	Yes	Anasarca	Not given	Gross dilatation. Hæmochromatosis of myocardium.
		54	M	Yes	Dyspnœa and œdema. Tearing substernal and left arm pain for 3 years, often on exertion.	Episode of Supraventricular tachycardia. Otherwise normal.	Dilatation. Hæmochromatosis of myocardium.
		34	F	No	Anasarca	Low voltage. Long P–R	Great dilatation. Hæmochromatosis of myocardium.
5	Maling and Riley, 1937	35	M	Yes	Agonizing pain behind sternum. Later auricular fibrillation and failure.	Low voltage. Flat T	Great enlargement. Diffuse fibrosis. Iron in muscle fibres, reticular cells and lying free.
6	Blumer and Nesbit, 1938	54	M	Yes	Substernal pain; relation to exertion not given. Œdema. Cardiac enlargement.	Not given	Intense pigment deposit. Increase of fibrous tissue. Coronary arteries moderately thickened. Slight intimal proliferation. No occlusion.
7	Petit, 1945	35	M	Yes	Dyspnœa. Œdema. Cardiac enlargement.	Complete A-V block. Inverted T in CR4.	Iron deposit. Areas of atrophy. Fibroblasts in empty spaces.
8	Tucker, Lloyd, and Williams, 1948	31	M	Yes	Palpitation. Dyspnœa. X-ray enlargement of heart.	Diphasic T I. Inverted T in CF4. Return to normal.	Dilated. Muscle fibres swollen. Pigmentation and fibrosis.
9	Horns, 1949	54	M	Yes	Attacks of præcordial pain for 3 weeks, 3 years before death. Not on exertion. Increasing dyspnœa and œdema.	1. Borderline QRS voltage. Isoelectric T I. (?) Diphasic T II. 2. Lower voltage. Diphasic T I and II.	Weight 440 g. Hypertrophy and dilatation. Pale staining and fragmentation of muscle fibres. Heavy infiltration of fibres with iron pigment. In some areas muscle substance seemed almost replaced.
10	Griffin, Nelson, and Seal, 1950	49	M	Yes	Dyspnœa. Œdema. Auricular fibrillation. X-ray enlargement of heart.	Auricular fibrillation. "Abnormal T waves."	Weight 667 g. Dilatation. Heavy iron deposit in muscle fibres. Interstitial fibrosis with iron in histiocytes.

Case Reports

Case 1. Man, aged 32. Buyer for National Coal Board. Subject to asthma from childhood. No other serious illness and not short of breath between attacks of asthma. In 1941 his family commented upon his dark skin; he did not think that the colour had darkened much since then. In 1946 he had two attacks of retrosternal and left-arm pain. After these he was seen by one of us (W.G.A.S.) for the Ministry of Pensions when a dusky colour was noted and the liver and spleen were found to be enlarged. The blood pressure then was 130/85 and the heart was normal on clinical and radiological examination. An electrocardiogram then showed normal voltage and an upright T in I, II, III, and CR4.

After this he remained well until April, 1950, when, while sitting, he experienced severe pain starting at the lower end of the sternum and passing up into the neck and jaws but not down the arms. There was also sharp pain in the right side which caught his breath. He became breathless and sweated. The pain lasted eight hours. One week later he was wakened by exactly the same pain which lasted four hours. Again, one week later, a severe attack of the same pain woke him at night. This lasted for ten hours and left an ache which persisted until the next day, May 1, 1950, when he was admitted to hospital. He stated that he was not losing weight, had no excessive thirst and had not lost libido. He denied alcoholic excess. He shaved daily.

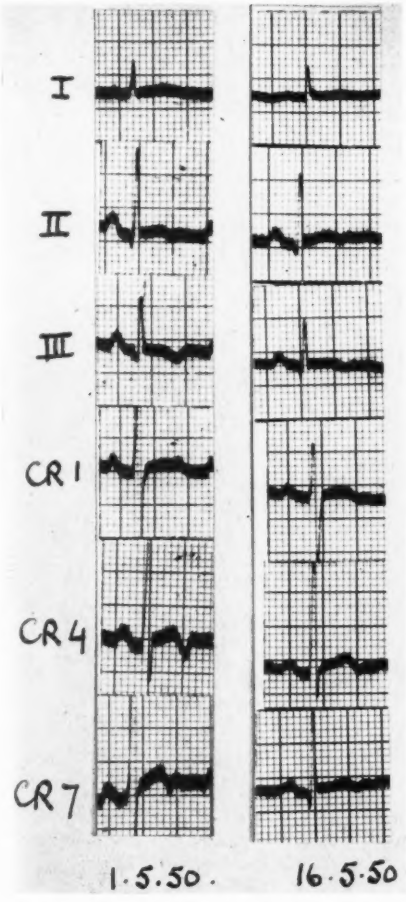

FIG. 1.—Case 1. Electrocardiograms showing S–T and T wave changes.

On admission he was noted to have uniform dark pigmentation of the skin over the whole body. The colour could best be called a leaden brown. The skin was fine and soft; there was no axillary hair and the pubic hair was scanty. His build was slender. The testes were not atrophied. There were no clinical signs of heart failure. The pulse was 90 and regular, and the blood pressure was 110/70.

The heart and lungs were normal clinically. The liver was enlarged four finger breadths, was very firm but not tender. The spleen was palpable on inspiration. The urine was free from sugar, acetone, and albumen.

Half-hourly sugar tolerance test. 0·132, 0·225, 0·290, 0·230, 0·175 mg. per 100 ml. No glycosuria.

Skin biopsy. There was iron-containing pigment immediately beneath the epidermis. It was mostly extra-cellular and some was in close apposition to the sweat glands.

Teleradiogram and fluoroscopy. Normal heart shadow. Normal lung fields.

Serial electrocardiograms (Fig. 1). Normal QRS voltage. S–T elevation and inversion of T in II, III, CR 4, and CR 7. T I almost iso-electric.

Progress. He had no further pain and he remains well at the time of writing. The electrocardiogram is changing slightly towards a more normal pattern.

Case 2. Man, aged 51. Coal miner. He was admitted to hospital on January 7, 1948, with a history that except for a hæmoptysis one year ago he had always

been healthy until six weeks before admission when he rather rapidly developed dyspnœa on exertion and swelling of the legs. Later he was breathless even at rest, especially at night. Soon after this thirst and polyuria appeared and he lost flesh rapidly, but the œdema went away.

On admission he was not in congestive failure but he looked thin and dehydrated. His lips were slightly cyanosed but neither skin nor mucous membranes were pigmented. The face, however, was strikingly smooth and he disclosed that for some years he had only needed to shave twice or thrice a week. Hair was absent from the axillæ and pubes and the penis was small. The left testis lay in the inguinal canal and the right, which lay in the scrotum, was obviously atrophied. The liver was enlarged two finger breadths below the costal margin and the spleen rather less; both were very firm. The urine contained sugar and acetone but no albumen.

Half-hourly sugar tolerance test. 0·22, 0·29, 0·40, 0·42, 0·40 mg. per 100 ml. No glycosuria except for a trace in the last sample.

Liver function tests. Thymol turbidity: 1 unit. Flocculation: 0 units. Alkaline phosphatase (Jenner and Kay): 9·2 units. Plasma proteins: 5·55 per cent; albumen, 4·08 per cent; globulin (by difference), 1·47 per cent. Hippuric acid excretion: 4 g. sodium benzoate ingested, 2·71 g. hippuric acid excreted (normal 3·2 g.).

Biopsy of liver: This showed essentially the appearances of a cirrhosis. The liver cells were stuffed with a pigment that gave a positive iron reaction—hæmosiderin. The appearances were compatible with the diagnosis of cirrhosis in a case of hæmochromatosis (Fig. 2).

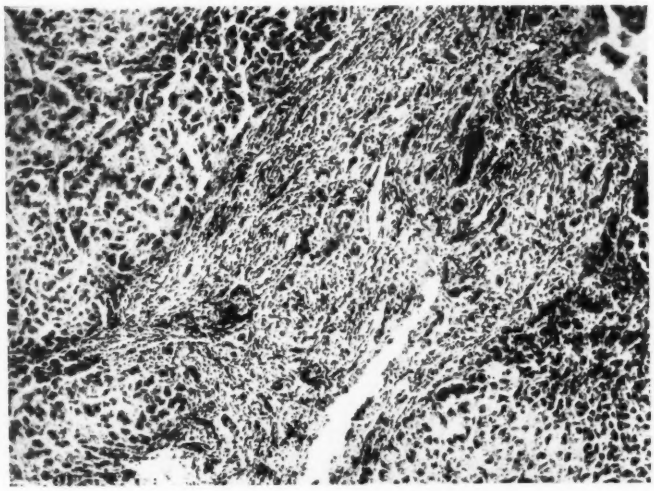

FIG. 2.—Case 2. Biopsy of liver, ×90. Stained for iron.

X-Ray of chest: No active lung lesion; calcified focus in right lower zone. Blood count: hæmoglobin 92 per cent; white cells 13,600 per c.mm. Basal metabolic rate: +18 per cent. Excretion of 17-ketosteroids: 2 mg. in 24 hours. Plasma sodium: 330 mg. per 100 ml. Kepler test: index 12.

He was stabilized on 160 g. carbohydrate with 10 and later 5 units of insulin twice daily. While in hospital his blood pressure fell and he developed congestive heart failure which improved with digitalis and mercurial diuretics so that he was discharged home eight weeks after admission. At home he gradually began to get about but after a few weeks dyspnœa increased and he was re-

admitted to hospital in congestive failure only two months after he had left. This time he did not improve and he developed lobar pneumonia. He recovered from this infection after treatment with penicillin but succumbed to heart failure three weeks after admission.

Cardiovascular features. At his first admission, although there were symptoms of cardiac insufficiency, he had no congestive failure. His pulse rate was 78 a minute and his blood pressure 120/80. Cardioscopy revealed some slight enlargement of the left ventricle but no other abnormality. The rhythm, however, was persistently irregular and a cardiogram (Fig. 3) showed this to be due to frequent extrasystoles, most of which arose from varying auricular foci, some from

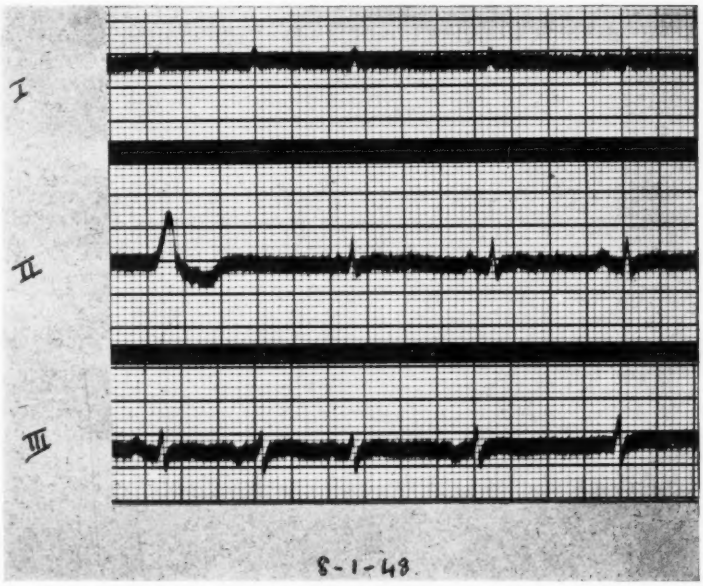

FIG. 3.—Case 2. Electrocardiogram showing low voltage QRS–T complexes and auricular and ventricular ectopic beats.

a ventricle. They continued with occasional intermissions until his death. This cardiogram showed also a very low voltage with slight elevation of S–T and flat T waves. CR leads taken one week later showed rounded elevation of S–T, maximal in CR 3 and 4, with sharp coronary type inversion of T in CR 4 to 6 (Fig. 4).

One week after admission the resting blood pressure had fallen to 82/70 and thereafter until his death the systolic pressure always lay between 95 and 75 and the diastolic between 80 and 66. On one occasion when the patient was stood up the systolic level rose to 95. Congestive failure gradually increased, the heart became moderately dilated and a soft systolic murmur appeared at the apex. The heart rate ranged from 80 to 90 a minute but decreased after digitalization to between 50 and 60. Fluids and salt were restricted and mercurial diuretics given. He improved on this regime and was free from œdema when discharged home, still on digitalis.

When re-admitted he was much more severely dyspnœic and more cyanosed. The neck veins showed mild engorgement and postural œdema was extensive. The heart was now very greatly dilated, its apex lying in the sixth space almost in the anterior axillary line. The rhythm was still predominantly irregular, the blood pressure was 95/70 and the rate 86 a minute. The

cardiogram (Fig. 5) was essentially the same but the voltage was lower than ever. Lobar pneumonia developed and he died in persisting congestive heart failure sixteen days after admission.

Necropsy (Dr. Ian Rannie). The *liver* weighed 2350 g. and showed moderate to severe cirrhosis with marked siderosis. The *spleen* contained practically no iron. The *pancreas* showed fibrosis

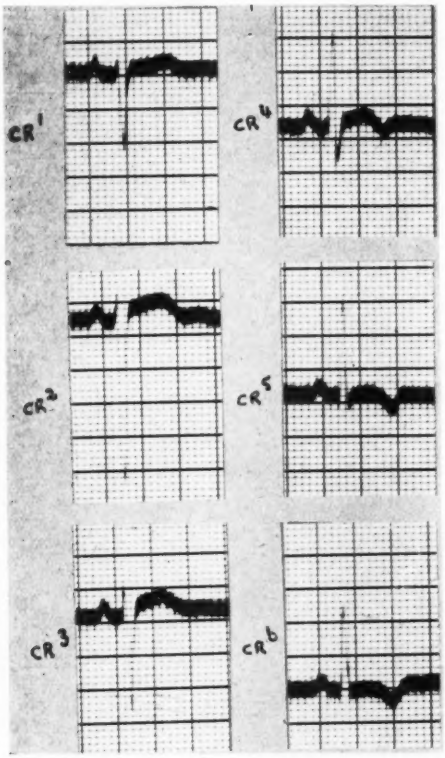

FIG. 4.—Case 2 (15/1/48). CR leads showing S–T and T wave changes.

and had iron in both acinar and islet tissue. The *skin* showed only slight iron pigment around the sweat glands. The *testes* were completely atrophied. The *pituitary* showed marked siderosis and a large scar from healed necrosis affecting the major part of one half of the anterior lobe but much glandular tissue remained. The *adrenals* showed reduction of cortex without much lipoid and with iron pigment, mainly in the outer part. The *heart* weighed 400 g. All the valves were healthy. Both auricles were dilated and both ventricles very greatly so. The myocardium measured 0·4 cm. at the base of the right ventricle and 1·2 cm. at the base of the left. The coronary arteries appeared to be healthy. There was an oval endocardial thickening measuring $1 \times 0{\cdot}5$ cm. on the interventricular septum.

On histological examination the myocardium showed a patchy siderosis, the iron pigment being present in the form of granules in the myocardial fibres. There was considerable destruction of muscle with replacement fibrosis and it was noted that this fibrosis was most marked in those areas

where the pigmentation of the muscle was most intense. Occasionally the pigment was seen to be in phagocytes in the interstitial tissue of the fibrotic areas but for the most part it was contained in the muscle cells themselves (Fig. 6 and 7).

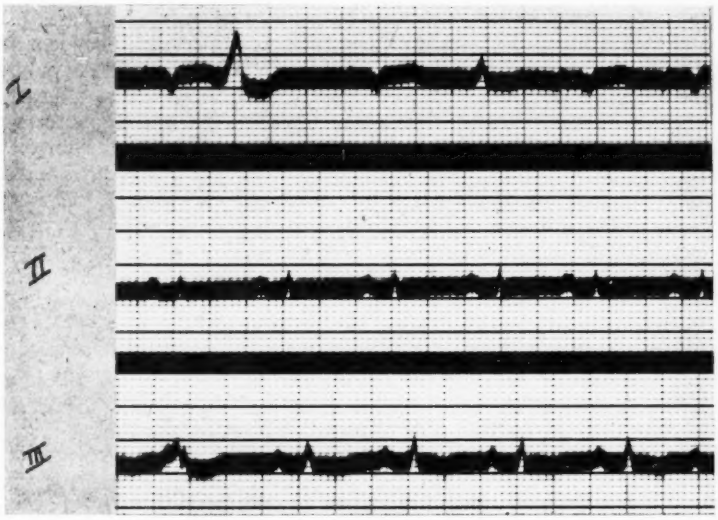

FIG. 5.—Case 2 (6/5/48). Electrocardiogram showing further lowering of voltage.

FIG. 6.—Case 2. Myocardium of ventricle, ×90. Stained with hæmatin and eosin.

FIG. 7.—Case 2. Myocardium of ventricle, ×90. Stained for iron.

Discussion

It is evident from the cases quoted and from our own experience that the cardiac manifestations of hæmochromatosis are not negligible and may even dominate the clinical picture. It is only in recent years that attention has been directed to the changes in the heart in this disease, and up to 1935 electrocardiographic observations had been made in only eight cases (Sheldon, 1935). It is consequently impossible to determine in what proportion of cases of hæmochromatosis clinical evidence of heart damage would be found while the patient is still alive. Recent publications suggest that this must be quite frequent and in all cases in which there was evidence of heart disease during life, necropsy showed extensive changes in the heart muscle. These changes seem to us to be an adequate explanation of the heart failure and do not justify the introduction of any endocrine factor. In particular the cardiac enlargement and the frequency of arrhythmias and of death in congestive failure are very unlike the circulatory features of Addison's disease. The variability of the cardiac findings, including as they do arrhythmias, conduction defects, and T wave changes, cardiac enlargement, and death in congestive failure seem to us to point to extensive damage to the heart muscle and all reports agree that there is no coronary insufficiency adequate to account for the atrophy of muscle and replacement fibrosis that has been described. The occurrence of pain identical with that seen in coronary artery disease is striking and perplexing. We have no explanation to offer for this interesting feature. It is of incidental interest that in hæmochromatosis the muscle of the heart should be so severely infiltrated with pigment when voluntary and plain muscle are relatively free. Sheldon has speculated that since the striped muscles most frequently used are those in which such pigmentation as occurs is most readily found, there may be some relationship between activity and pigment deposition.

Summary

Previously reported cases of cardiac involvement in hæmochromatosis are reviewed. Two cases are described in one of which there was cardiac pain and T wave changes; in the other, death from congestive cardiac failure occurred with gross cardiac enlargement, electrocardiographic abnormalities, and severe hæmochromatosis of the myocardium.

It is felt that the explanation for the observed changes is most probably the deposition of pigment in the myocardium and not any endocrine factor.

Our thanks are due to Dr. C. N. Armstrong for permission to publish Case 2 and to Dr. I. Rannie for his report of the necropsy of this case.

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THE CARDIOGRAM IN VENTRICULAR ANEURYSM FOLLOWING CARDIAC INFARCTION

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The most reliable single aid in the diagnosis of ventricular aneurysm is fluoroscopy and the value and difficulties of this method of diagnosis have been fully dealt with by Parkinson *et al.* (1938). If one accepts the definition of Matthew Baillie (1793), which runs " This disease consists in a part of it (the heart) being dilated into a pouch which is commonly more or less filled with coagulated blood," those cases that show merely an excavation of the inner surface of the ventricle should be excluded: they would not be diagnosed by fluoroscopy. There is no doubt that ventricular aneurysm can be present and yet careful rotation of the patient at fluoroscopy may show only an enlarged left ventricle. On the other hand, what is considered to be radiological evidence of ventricular aneurysm may be found to have been misleading (see Case 7) and even when radiological signs of aneurysm appear to be present they may be only transient (see Case 4). The radiological diagnosis of posterior cardiac aneurysm is particularly difficult, and we have been able to find very few convincing illustrations.

There is thus a need for some other aid in the diagnosis of ventricular aneurysm following cardiac infarction and according to Samet *et al.* (1950) the electrokymogram may soon prove of value. In the meantime, there is no doubt that a striking divergence of opinion exists concerning the value of the cardiogram in the diagnosis of ventricular aneurysm, as recently revealed by Rosenberg and Messinger (1949).

Naturally we wondered whether some of the cardiographic appearances said to be suggestive or typical of ventricular aneurysm could not in fact have been produced by large transmural infarcts not necessarily accompanied by any bulging. After all, as pointed out by Gross and Schwedel (1941), the resilience of the resulting scar depends on many factors, such as the size of the area infarcted, the site of the infarct, and the presence or absence of intramural thrombus, calcification, or possibly pericardial adhesions. Perhaps the intraventricular pressure may count as well. We feel that probably the most important cause is the extent to which a large infarct has involved the thickness of the ventricular wall and there is some cardiographic support for this opinion in the form of QS waves. In order to decide whether these so-called typical appearances of aneurysm were due merely to the presence of a large transmural infarct, with or without aneurysm formation, we have compared two distinct types of case. The first group consisted of patients in whom there was evidence of cardiac aneurysm either at autopsy or radiologically: the second, of patients in whom there was a large transmural infarct of the left ventricle and yet at autopsy it was noted that no aneurysm was present. We have also included some details of a much smaller group where no autopsy was obtained and the radiological appearance, coupled with the clinical findings, made the diagnosis of ventricular aneurysm likely but not certain. A point of some importance that we would wish to emphasize, is that search for ventricular aneurysm must be made when the material is fresh. It is surprising how shrinkage due to formalin can reduce the dimensions of an aneurysmal

bulge or obliterate it altogether unless the clot is removed and the cavity packed with cotton wool before fixation.

Material and Results

We divided our material, consisting of 42 cases, into three groups (see Table). First, those in which a diagnosis of ventricular aneurysm was considered to be certain: there were 27 cases; in 11 autopsy confirmed the presence of ventricular aneurysm, and in the remaining 16 the radiological appearance was beyond doubt (Fig. 1). Secondly, a group of 12 cases in which at autopsy a large transmural infarct was present but gave rise to no ventricular aneurysm. Thirdly, 3 cases where the presence of ventricular aneurysm was suspected clinically and radiologically but we could not be certain that one was present and no autopsy was obtained.

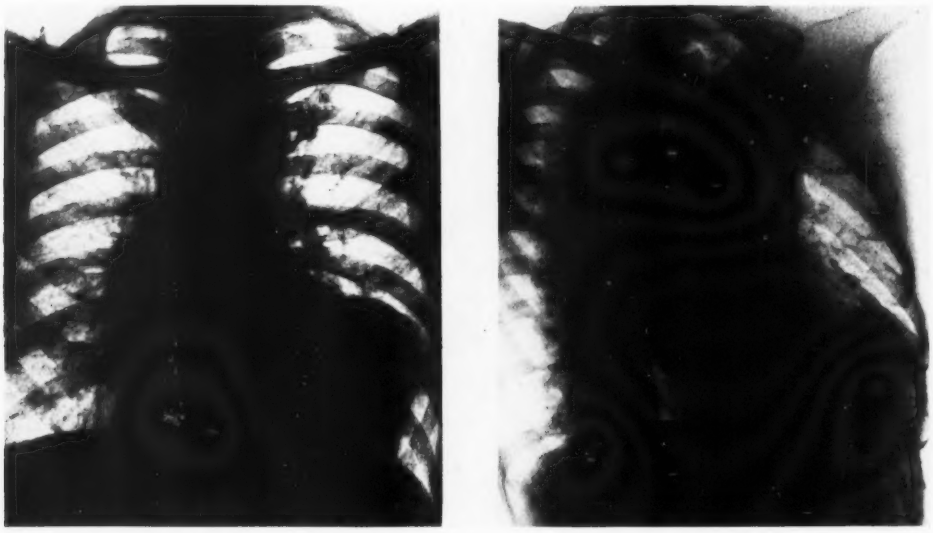

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Fig. 1.—Case 1. (A) Antero-posterior view. (B) Right anterior oblique view. Large ventricular aneurysm present.

Of the group known to have a ventricular aneurysm, it was anterior in 24 and postero-apical in 3 cases. No case of a purely posterior infarct leading to aneurysm was encountered for the T waves in the leads from the left of the præcordium were also inverted.

Of the 12 cases with large infarcts without aneurysm 9 were anterior, 2 were both anterior and posterior, and 1 was entirely posterior. All of the three suspected but unconfirmed cases of aneurysm were thought to be anterior.

Ventricular Aneurysm

On analysing the curves obtained from the 24 examples of cardiac aneurysm arising from *anterior infarction*, it at once became obvious that a certain pattern was common. Not only is the pattern frequently seen, but once it appears it persists. It consists of the following features.

In the Chest Leads

(1) The presence of a QS wave (R being absent) in at least one (V1 excluded) of the unipolar chest leads.

TABLE I

SUMMARY OF MATERIAL

Type of Case	Total	Autopsy	Radiology	Site of Cardiac Aneurysm or Infarct			
				Anterior	Posterior	Anterior and posterior	Postero-apical
Proven aneurysm	27	11		10*			1
			16	14			2
Suspected aneurysm	3		3	3			
Infarct without aneurysm	12	12		9	1	2	

* One of these cases had two anterior infarcts, only one of which had led to aneurysm formation. In another anterior case the infarct had also resulted in an aneurysm of the ventricular septum.

(2) Elevation of the RS–T segment in the unipolar chest leads, this being variable in occurrence and duration.

(3) Widespread inversion of the T wave, or its incorporation in the elevated RS–T segment, in at least three of the unipolar chest leads.

In the Limb Leads

(4) A Q wave in VL, and therefore in standard lead I.

(5) Inversion of the T wave in VL, and consequently in standard lead I.

(6) A deep S wave in VF, 5 mm. or more in depth, and consequently in standard leads II and III.

Four of these six features were constantly present in no fewer than 18 of the 24 cases, namely (1) one or more QS waves, (3) widespread inversion of the T wave in the chest leads, (5) inversion of the T in VL, and (6) a deep S wave in VF (Fig. 2). The two inconstant features were a Q wave in VL which was present in 15 of the 18 cases; and elevation of the RS–T segment which occurred in 12 of the 18 cases, but in 3 of the 12 it was of short duration only. We consider that undue emphasis has been placed on the presence and persistence of RS–T segment elevation in the diagnosis of cardiac aneurysm. It is often absent in cardiac aneurysm, and can be present and persist in large antero-lateral infarcts in the absence of aneurysm formation.

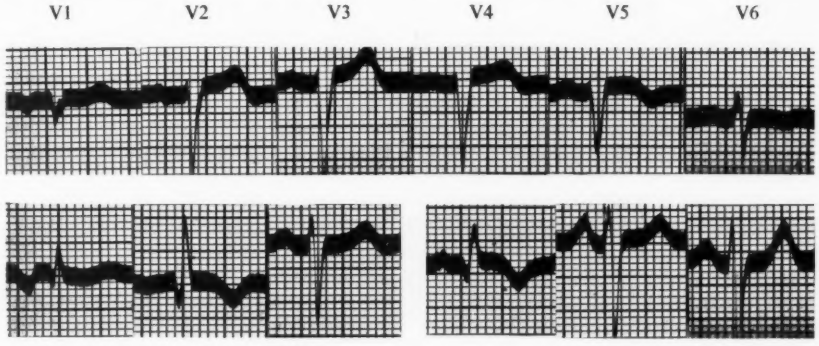

FIG. 2.—Case 1. The four features of ventricular aneurysm are the presence of a QS wave in at least one of the unipolar chest leads, inversion of the T wave in some of the chest leads, inversion of the T wave in leads VL and I, and a deep S wave in leads VF, II, and III. In addition a Q wave is present in leads VL and I.

Of the remaining 6 cases out of the 24, four had a QS wave in standard lead I, and two of these showed a deep S in VF, and thus in standard leads II and III, with extensive inversion of the T wave in the chest leads. The other two with QS waves in standard lead I had no such deep S waves in VF, II, or III, but had inversion of the T waves in the chest leads. The fifth case resembled the 18 " typical " cases with a Q wave and an inverted T wave in leads VL and I and extensive inversion in the chest leads, except that there was no S wave in leads VF, II, or III. This is the only example we have been able to find of such a curve in the presence of anterior ventricular aneurysm. The electrocardiogram and radiological appearance are illustrated in Fig. 3 and 4 (Case 2) and will be commented upon later. The sixth case had all the " typical " cardiographic features except that the S wave in standard lead II was absent.

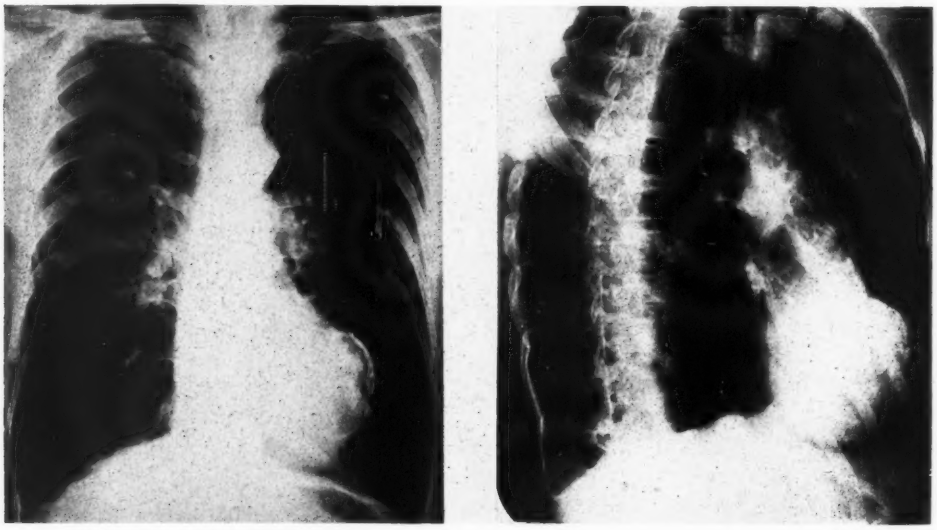

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FIG. 3.—Case 2. (A) Antero-posterior view. (B) Right anterior oblique view. Calcified aneurysm of left ventricle.

The curves from the three cases of *postero-apical infarction* with posterior aneurysm did not reveal any features other than those to be expected from a transmural infarct, except that, as already mentioned, all three were postero-apical and not just posterior. All three had a QS wave in VF. None of them showed well developed elevation of the RS–T segment; in two of them we took œsophageal leads and no such elevation was seen in those leads either, nor was any further clue as to the presence of aneurysm obtained.

Of the three doubtful cases of aneurysm two had the six typical features mentioned above, and, although radiologically we could not be certain of an aneurysm, we felt it almost certainly was present in the two with that type of cardiogram. The other doubtful case was probably not one of cardiac aneurysm, as the cardiogram was within normal limits in spite of the suggestive radiological appearance (see Case 7, Fig. 11 and 12).

INFARCTION WITHOUT ANEURYSM

Of the 12 examples of large transmural infarct without aneurysm, nine were anterior, one was posterior, and two were both anterior and posterior.

When we considered the curves obtained from the nine extensive anterior infarcts without aneurysm formation, we were surprised to see that in none of them did the curves show all the four criteria mentioned previously, namely (1) the presence of one or more QS waves, (3) widespread inversion of the T wave in the chest leads, (5) inversion of the T wave in VL, and (6) a deep S wave in VF. In one case only (Case 9, Fig. 14) did the cardiographic appearances resemble these criteria, and that was an example where at autopsy in addition to a large anterior infarct a recent posterior infarct was also present. Of the nine anterior cases, eight showed the usual changes in the chest leads of anterior cardiac infarction but without the other criteria of aneurysm in the unipolar limb leads that we have described; and in the other case the appearance was obscured by auricular flutter with 1: 2 ventricular response. In two of the eight cases, however, there was a deep S in

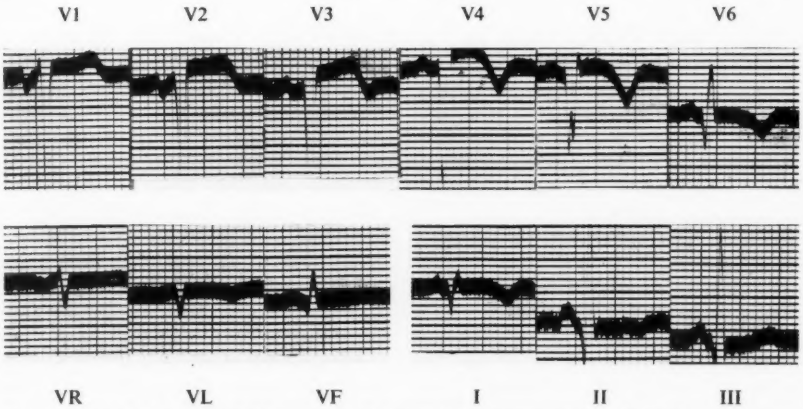

FIG. 4.—Case 2. In spite of the presence of a ventricular aneurysm (Fig. 3) there is no S wave in leads VF, II or III.

VF, and so in standard leads II and III; but in one of these the chest lead T waves were not inverted, and in the other no chest leads were taken.

The biggest series of large antero-lateral infarcts that has been fully explored cardiographically and correlated at autopsy is that of Myers *et al.* (1948). They give details of 57 such cases and from study of their illustrations, provided recent infarction is excluded, we were unable to find an example showing all of the six cardiographic features we have described, except when a cardiac aneurysm was present. Of their four examples of actual cardiac aneurysm, three showed the appearance such as we have noted (their Fig. 15).

The example of large posterior infarct without aneurysm could not be distinguished cardiographically, even with œsophageal leads, from the three that had a posterior aneurysm at autopsy, except that in the aneurysm cases the inversion of the T wave had spread round to the front of the left ventricle whereas it had not done so in the posterior infarct case without aneurysm.

ILLUSTRATIVE CASES

Case 1. Male, aged 64. History of cardiac infarction with pain lasting four hours, development of a pericardial rub on the third day, and later appearance of left ventricular gallop rhythm. The cardiogram (Fig. 2) showed the six typical features of aneurysm that we have described. Although no autopsy was obtained there is no doubt from the X-ray appearance (Fig. 1) that a large ventricular aneurysm was present.

Case 2. Male, aged 60. This large ventricular aneurysm with calcification of its wall (Fig. 3) is one of the few examples where the S wave was absent in leads VF, II, and III (Fig. 4). In spite of the absence of pain in the chest for twenty-two years, considerable RS–T elevation persists in leads V2 to V5 and a QS wave is present also in those leads. We are grateful to Dr. G. A. Kiloh for details of this patient.

Case 3. Male, aged 72. A large cardiac aneurysm at autopsy had caused such thinning of the left ventricular wall that on removing the clot from the aneurysm light could be seen through it. The cardiogram (Fig. 5) was unusual in that, in addition to the absence of a Q wave in leads VL and I, no R wave was present in VR, although according to Goldberger and Schwartz (1948) this would indicate the absence of ventricular aneurysm. The aneurysm had caused a peculiar elongation of the left ventricle (Fig. 6) as originally described by Hochrein (1932).

Case 4. Male, aged 55. This illustrates how the radiological appearances can be deceptively transient in the presence of cardiac aneurysm. On 16/8/50 an adhesion was present near the apex of the left ventricle (Fig. 7) and the cardiogram (Fig. 8) showed QS waves in leads V1 to V3, elevation of the RS–T segment in V1 to V4, inversion of the T wave in leads V3 to V6, as well as the QI, TI, SVF, SII and SIII appearance in

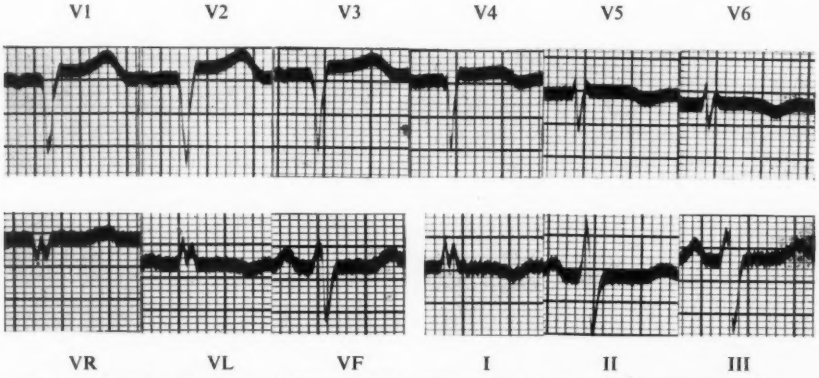

FIG. 5.—Case 3. The unusual features of this cardiogram of a ventricular aneurysm (Fig. 6 (A) and (B)) are the absence of an R wave in lead VR and of a Q wave in leads VL and I.

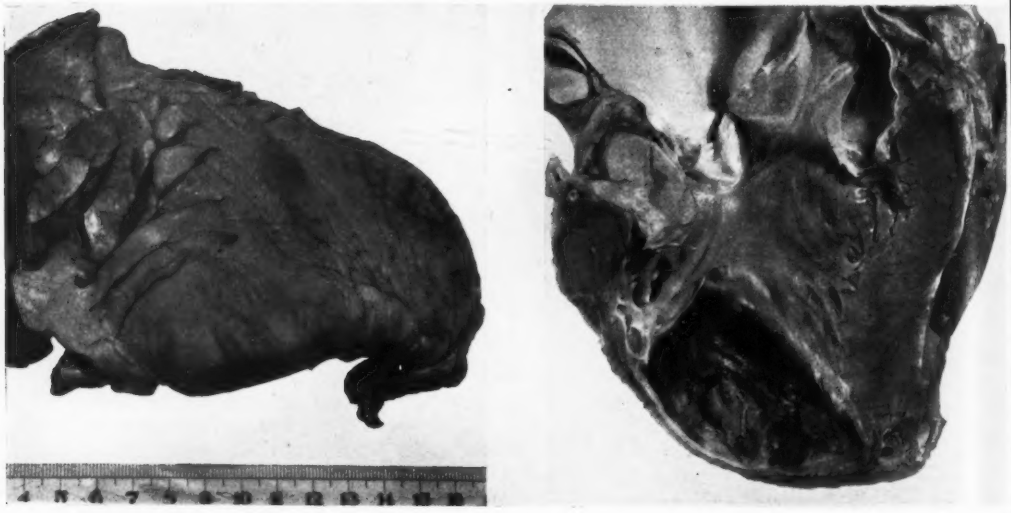

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FIG. 6.—Case 3. (A) and (B) show elongation of the left ventricle resulting from ventricular aneurysm.

the limb leads, all suggesting anterior aneurysm. However, by 2/11/50 the appearance at the apex had altered and the left ventricular contour was smooth in all positions at fluoroscopy (Fig. 7). We presume that the appearance of 16/8/50 was due to an adhesion overlying the ventricular aneurysm which some time between that date and 2/11/50 had broken down. The patient had an apex beat suggestive of cardiac aneurysm in that two distinct and slightly asynchronous thrusts could be felt in the region of his apex a little outside the left mid-clavicular line.

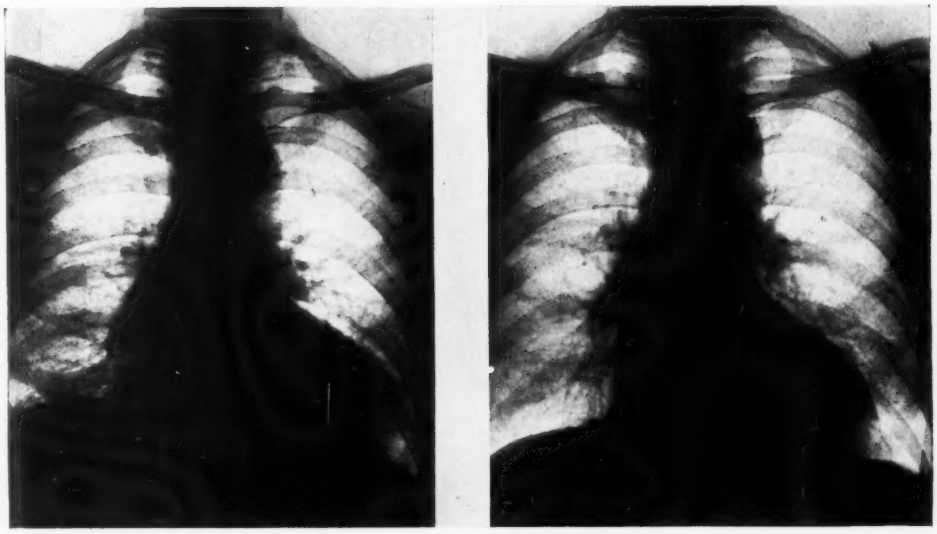

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FIG. 7.—Case 4. (A) Antero-posterior view taken on 16/8/50. An adhesion is present near the apex of the left ventricle. (B) Same view taken on 2/11/50. The left ventricular contour is smooth.

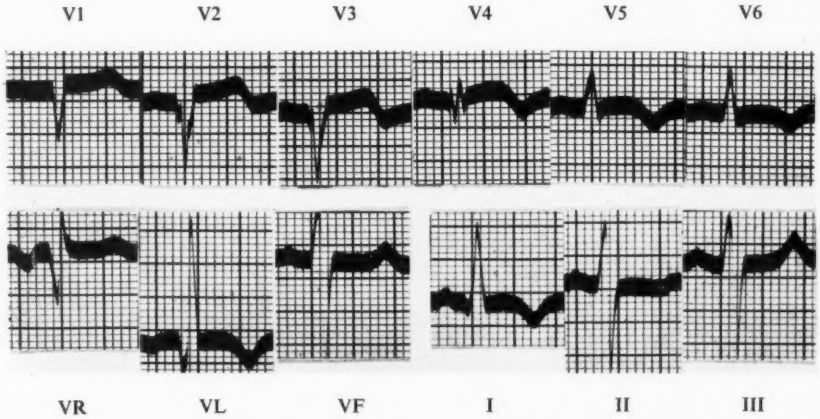

FIG. 8.—Case 4. Cardiogram of ventricular aneurysm in spite of the radiological appearance of Fig. 7 (B), namely one or more QS waves and widespread inversion of the T wave in the chest leads, inversion of T in VL and I, and a deep S wave in leads VF, II, and III.

Case 5, male, aged 58, and *Case* 6, male aged 41. These two examples illustrate the persistence of considerable elevation of the RS–T segment which is sometimes found. In Case 5 the patient had experienced no cardiac pain for the previous two years and in the right oblique view a ventricular aneurysm was seen. In addition to the other cardiographic features of aneurysm there was considerable RS–T segment elevation in leads V2 to V5 (Fig. 9). Case 6 had had his infarct four and a half months prior to the cardiogram illustrated (Fig. 10) and at fluoroscopy on the same day as the cardiogram a localized area of paradoxical pulsation was seen 1 cm. above the apex of the heart. The record illustrates well the RS–T segment elevation which is seen in leads V2 to V5 and it is also a good example of the presence of QS waves in the chest leads—in this case in leads V1 to V5 inclusive. The other appearances associated with an aneurysm are also seen.

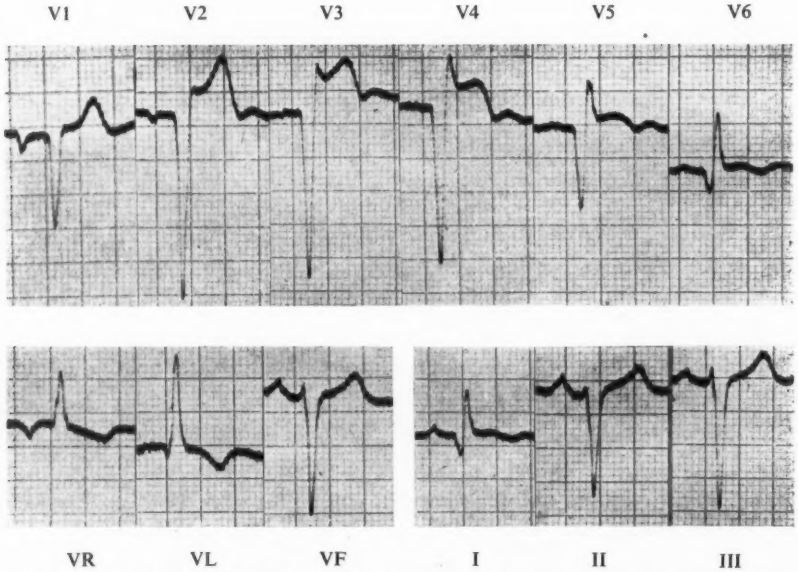

FIG. 9.—Case 5. In addition to the four commonest features of ventricular aneurysm (see text), and the presence of a Q wave in leads VL and I, considerable elevation of the RS–T segment is seen and has been present for two years.

Case 7. Male, aged 58. This is an example where the radiological evidence was again probably misleading (Fig. 11). The patient had severe sub-sternal pain in April, 1944, and clinically there was separate pulsation in two nearby areas near the left nipple. However, his cardiogram taken on the same day as Fig. 12 did not confirm the presence of an extensive infarct. A second twelve-lead cardiogram taken a year later showed no alteration. We therefore doubt whether the radiological appearance was that of ventricular aneurysm. Pericardial adhesions which distort the shadows of the left ventricular border are not uncommon in the absence of aneurysm (Schwedel, 1948).

Case 8. Male, aged 53. This patient is also one from our doubtful group. The cardiographic appearances were strongly suggestive of the presence of a ventricular aneurysm, namely the presence of a QS wave in lead V2 with T wave inversion in leads V2, V5, and V6, with a deep S wave in VF and thus in SII and SIII, together with a Q wave and inverted T wave in leads VL and I. Fluoroscopy did not reveal an aneurysm, and final diagnosis must await autopsy. As only lead V2 shows a QS wave (Fig. 13) it is possible that an aneurysm was present but was too small and too anterior to be demonstrated at fluoroscopy.

Case 9. Female, aged 62. In spite of the presence of an extensive anterior infarct with also a recent large posterior infarct high up in the septum, and the cardiographic appearances somewhat resembling those such as we found accompanying aneurysm, autopsy revealed no evidence of a local bulge. It will be seen (Fig. 14) that the T wave is inverted in leads V2 to V6 inclusive and in leads VL and standard lead I, and that

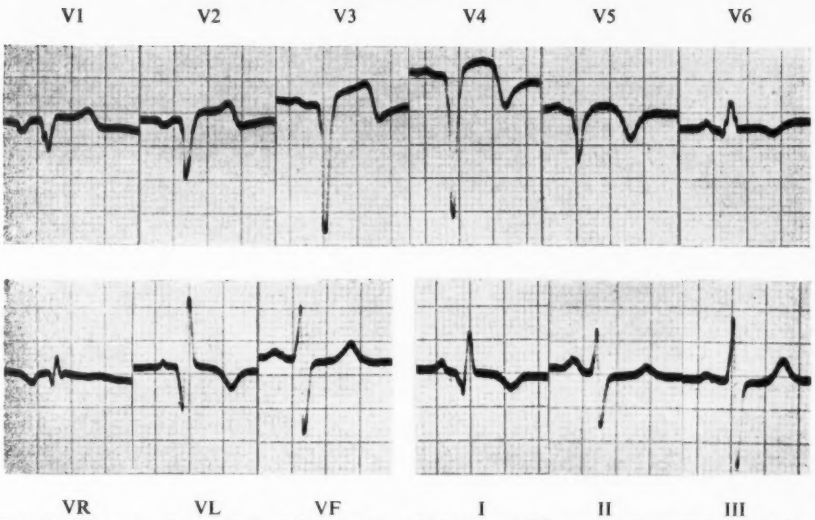

FIG. 10.—Case 6. An example of the presence of widespread QS waves and persistent elevation of the RS–T segment in the chest leads in ventricular aneurysm.

FIG. 11.—Case 7. Ventricular aneurysm was suspected because of a history of severe substernal pain, the presence of two separate impulses near the left nipple, and paradoxical pulsation of the left ventricular border. However, the cardiogram was not consistent with that diagnosis (Fig. 12).

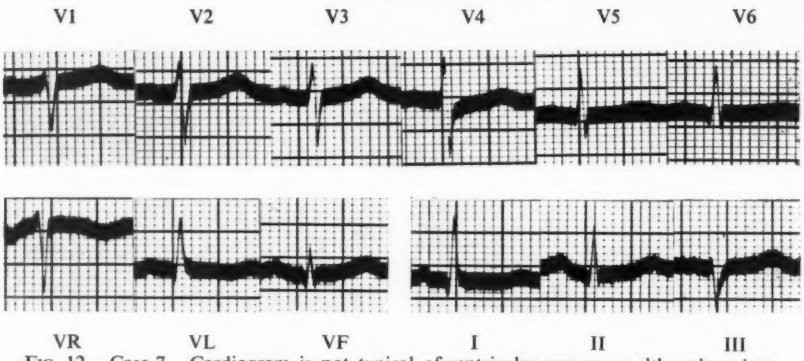

FIG. 12.—Case 7. Cardiogram is not typical of ventricular aneurysm although perhaps suggestive of some ischæmia of the left ventricle.

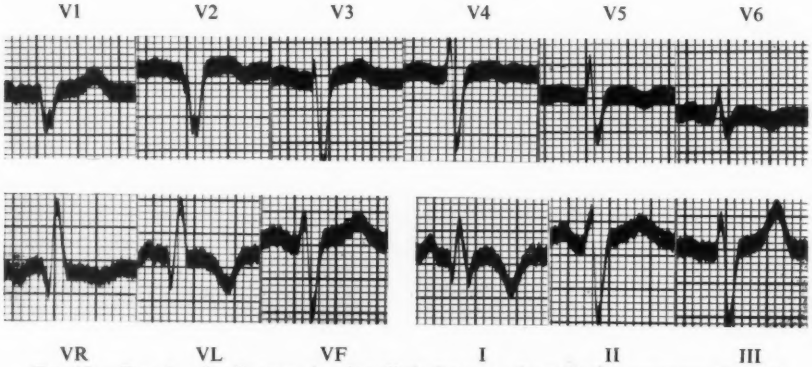

FIG. 13.—Case 8. Cardiogram showing all six features of ventricular aneurysm (see text) yet fluoroscopy failed to confirm its presence.

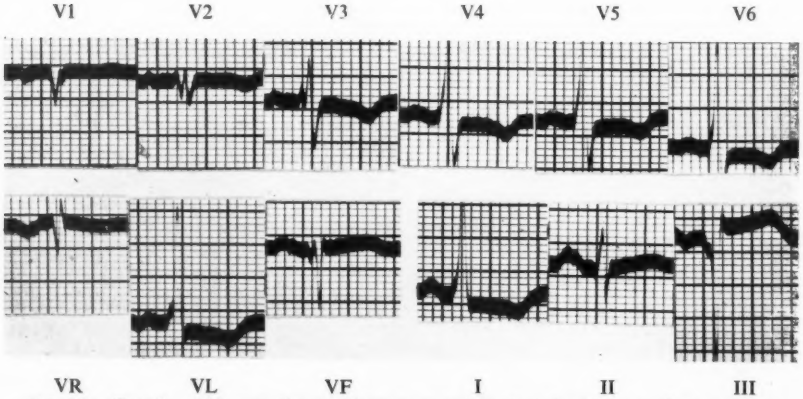

FIG. 14.—Case 9. Although the cardiogram resembles that found in cardiac aneurysm none was present at autopsy. The asymmetrical inverted T wave and depression of the RS–T segment in leads VL, I, and the chest leads suggest that left ventricular hypertrophy is contributing to the record.

a deep S wave is present in leads VF and standard leads II and III. But the RS–T segment is depressed in lead I and elevated in lead III and we consider that at least some of this appearance is due to left ventricular hypertrophy (the heart weighed 507 g.), and the deeply negative complex in lead VF and III almost certainly represents a QS wave due to the large recent posterior infarct in addition to the old anterior one.

Discussion

Nordenfelt (1939) seems to have been the first to investigate the problem as to whether a ventricular aneurysm gave cardiographic changes peculiar to itself as opposed to those resulting from infarction without aneurysm. He stated that large aneurysms of the anterior wall of the left ventricle gave a relatively low R wave in lead I with a negative or isoelectric T wave in that lead, a deep S wave in standard leads II and III with a positive T wave in those leads. He stated that a clear QI occurred also, and that in IVR there was a deep S (QS) wave and that the RS–T segment was somewhat elevated. Actually a few years earlier than this Sigler and Schneider (1935) were the first to point out that in apical aneurysms there was a tendency for the major QRS deflections to be deflected downwards in lead II and III. Apart from Nordenfelt's emphasis on the low R wave in standard lead I, which in our records is commonly tall, as well as in VL, we would agree that the QI, TI, SII, SIII appearance is in itself most suggestive of a cardiac aneurysm, although it is true that this appearance may occur without aneurysm. Such deflections were seen in no fewer than 18 of our 24 proven anterior aneurysm cases, and if a QS wave is accepted instead of a Q wave then the figure of 18 rises to 20. But these deflections were also seen in two of the nine cases of anterior infarct where no aneurysm was present at autopsy.

In the same year as Nordenfelt's paper, Eliaser and Konigsberg (1939) stated that the cardiograms obtained from cases of ventricular aneurysm could be considered as falling into four groups. Their first group showed what they termed left axis deviation, and corresponds fairly closely to the one mentioned by Nordenfelt. They thought that the cardiogram was not peculiar to cardiac aneurysm but occurred sufficiently often to warrant consideration of it. Their second group showed what they termed right axis deviation, with a large S wave in lead I accompanied by an inverted T wave in that lead. It can be seen from their illustrations that this so-called S wave is in fact a QS wave and that the R wave is absent. This apparent right axis deviation is really due to the fact that VL records the cavity potential from inside the left ventricle (QS) owing to the death of the intervening muscle tissue. As we have said, we encountered four such aneurysms where there was a QS wave in lead VL, and thus also in lead I, and none of the ten cases of anterior infarction without aneurysm showed such a QS wave. Rowland (1943) even states that when this " right axis deviation " appearance is present it is of greater diagnostic value than the TI, SII, SIII type of curve. Gross and Schwedel (1941) also conclude that the single positive finding in ventricular aneurysm is the comparative frequency of " right axis deviation." Recently Laham (1950) has stated that this appearance of right axis deviation is the commonest finding in ventricular aneurysm. We would agree that the absence of an R wave in standard lead I with the production of a QS wave in that lead is in itself highly suggestive of the presence of an anterior aneurysm, but in our experience it is not the commonest cardiographic appearance to accompany ventricular aneurysm.

Dressler and Pfeiffer (1940) were the first to point out that the cardiographic changes once developed appeared to be very constant, and a deep S deflection in leads II and III was striking in half their cases. Boyd and Scherf (1942) were the first to draw attention to the fact that the elevation of the RS–T segment was such that one was inclined to assume that a recent infarct had occurred but that when these cases of aneurysm were followed the cardiogram was found to retain the same appearance for years.

Wilson *et al.* (1944) confirmed the observation of Boyd and Scherf and extended it to include unipolar chest leads. They could offer no explanation as to why this persistent RS–T segment displacement should be present and thought it was merely a chance association with aneurysm. Later, however, Wilson *et al.* (1947) held the opinion that this permanent RS–T segment displace-

ment was associated with ventricular aneurysm more often than one might suspect. This may well be the case, for the important lesion is the large infarct. Myers *et al.* (1948) had previously pointed out that this tendency for the persistence of the RS–T segment elevation in cardiac aneurysm rendered it impossible to estimate the age of an infarct from the study of one tracing without other clinical details. They thought the abnormal RS–T segment and T wave probably represented cavity potential transmitted through the aneurysm without modification when the wall was completely replaced by fibrous tissue, or transmitted with slight alteration when the wall contained some remnants of muscle. They also pointed out that in addition to ventricular aneurysm causing segment shift very like a recent infarct, two other conditions could lead to similar changes, namely the occurrence of pericarditis independent of an old healed infarct, and the effect of cardiac glycoside superimposed on the curve due to an old healed infarct. The effect of digitalis on the RS–T segment and T wave depends upon the direction of the major phase of the QRS. In leads with a QS complex and upright T wave, full digitalization may result in further elevation of the RS–T segment and increased amplitude of the T wave. Rosenberg and Messinger (1949) have recently pointed out that in cases with bundle branch block the persistence of the RS–T segment elevation in chest leads does not, of course, have the same significance as in cases where there is no block. Ford and Levine (1949) confirmed the opinion of Wilson and his co-workers that persistent elevation of the RS–T segment, although non-specific, should lead the clinician to suspect the presence of ventricular aneurysm; it was present in seven of their ten cases.

While agreeing that persistent elevation of the RS–T segment is suggestive of cardiac aneurysm, we feel that it has perhaps been over emphasized. There seems no general agreement as to how long the RS–T segment elevation can persist in the absence of cardiac aneurysm. There was no segment elevation in 6 of our 24 proven anterior aneurysms. However, if the segment elevation is very great, say more than 5 mm. in some chest leads, and persists for a matter of several months or more, especially if associated with QS waves across the chest, then in our opinion this is very strong evidence indeed of cardiac aneurysm (see Cases 5 and 6, Fig. 9 and 10). The cause of this elevation of the RS–T segment remains obscure. The explanation of Moyer and Hiller (1951) that elevation of the RS–T segment that persists long after the stage of injury is caused by hypertrophy of the posterior wall of the heart opposite to the lesion, exerting its effect through dead intervening tissue, is attractive. Hypertrophy of the left ventricle was present in 7 of our 11 autopsy cases with aneurysm. The weight of the heart was recorded in five, namely 480, 500, 615, 850, and 885 grammes, and it is interesting to note that the greatest segment elevation was seen in the heaviest heart.

Goldberger and Schwartz (1948) claim that the QRS is upward in VR when ventricular aneurysm is present, and that the absence of this feature excludes the lesion. Our records do not entirely support this view, for in 7 of our 27 proven cases the R wave in VR was tiny, being less than 1 mm. and in one case it was absent altogether (Case 3, Fig. 5). But the fact that it may occur, perhaps from a change of position, fits in with the next point.

We consider that the S wave in VF, and consequently in standard leads II and III, is the important sign, for it determines the form of the bipolar limb leads. This deflection, more than 5 mm. deep, was present in no fewer than 18 of our 24 cases of proven aneurysm. In all these where VF showed a deep S wave, VL showed a tall R wave (over 5 mm.). This finding would show that the unipolar limb leads indicate an electrically horizontal heart when aneurysm results from anterior infarction.

Summary and Conclusions

If cardiographic appearances such as we have described are encountered, then provided there is no reason to suspect that the infarct is recent or that digitalis is affecting the cardiogram or that recent pericarditis has occurred, an anterior cardiac aneurysm is likely to be found at autopsy.

The four essential features are: (1) the presence of QS waves in one or more chest leads (ex-

cluding VI); (2) inversion of the T wave, or its incorporation in the elevated RS–T segment, in at least three of the unipolar chest leads; (3) the presence of a deep S wave in lead VF, at least 5 mm. in depth, and consequently in standard leads II and III also; (4) inversion of the T wave in VL and therefore also in standard lead I. Two other very common but not essential points are persistent elevation of the RS–T segment in unipolar chest leads and the presence of a Q wave in lead VL and thus in standard lead I.

These were the findings in 18 out of 24 anterior aneurysms, and in a total of 20 if a QS wave instead of a Q wave is included in lead VL and standard lead I. Once these cardiographic appearances have developed they appear to be constant.

We do not, of course, claim that all anterior cardiac aneurysms produce this appearance and examples are quoted and illustrated where it is absent. However, when it is present this appearance is so highly suggestive, if not pathognomic, of cardiac aneurysm that it should lead to very careful fluoroscopic search for the presence of one. In three of our cases the ventricular aneurysm was unsuspected radiologically but more careful search as a result of the cardiographic appearance confirmed the presence of an aneurysm. In a fourth case, a large and persistent pleural transudate due to heart failure obscured the left border of the heart until death but the presence of a ventricular aneurysm was confidently diagnosed from the cardiogram and was subsequently confirmed at autopsy.

In spite of statements to the contrary, the presence of aneurysm is compatible with the absence of an R wave in unipolar limb lead VR and one such case is illustrated.

We could find no cardiographic evidence diagnostic of the presence of a posterior cardiac aneurysm, including œsophageal leads in two cases, but in all three of our examples of posterior aneurysm the cardiogram showed that the damage had also extended round to involve the apex of the heart, and a QS wave was present in lead VF. A septal aneurysm was present in one anterior case but there was no cardiographic evidence to suggest this.

It might be thought that any large transmural antero-lateral infarct would give rise to an appearance such as we have described, but it was not found in ten such cases where aneurysm was excluded at autopsy, and this is in keeping with the results of other workers who have correlated closely the cardiogram and morbid anatomy of the infarct. Although the features of the chest leads can be the same in large anterior infarcts with or without aneurysmal bulging, when the limb leads are also included such an appearance as we have described as common in cardiac aneurysm is most unlikely to result from an old antero-lateral infarct without the formation of an aneurysm.

The final *conclusion* of this study would be that as far as the chest leads are concerned, large anterior infarcts and aneurysms resulting from large anterior infarcts resemble one another, and this is what one would expect. There is no particular reason why a dead fibrotic ventricular wall that is thin enough to bulge and become an aneurysm should give rise to chest lead cardiograms peculiar to itself and distinct from a large transmural infarct that does not bulge. In either case the cardiograms may remain unchanged for years.

The cardiographic difference between aneurysmal and non-aneurysmal infarcts seems to be more in the limb leads. To some degree the interception of cavity potentials by lead VL will have its effect here, and so cause the important and characteristic QS in standard lead I. But apart from this the question of the electrical position of the heart arises. We think that for some reason the presence of a ventricular aneurysm seems to affect this position and causes a deep S wave in VF which appears also in standard leads II and III.

To understand the reason for certain cardiographic appearances is interesting and useful. But when they help the diagnosis of ventricular aneurysm we wonder whether it is important. These lesions do not seem to carry any worse prognosis than other large infarcts. We regard them as more curious than lethal. The ultimate outlook for the patient depends on the fate of the muscle that survives, not on the loss of the muscle that has died.

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CASE REPORTS

EPILEPTIFORM ATTACKS DUE TO MYXOMA OF THE RIGHT AURICLE

BY

DAVID KENDALL AND BRUCE SYMONDS

Attacks of dizziness and syncope have been relatively common features in the recorded cases of primary intracardiac tumour and of intracardiac ball thrombus (Wood, 1814; von Recklinghausen, 1885; Schwarz and Biloon, 1931; Gorlitzer, 1934; Elson, 1934; Fawcett and Ward, 1939; Garvin, 1941; Wright, Flynn, and Druet, 1944; Burnett and Davidson, 1945; Evans and Benson, 1948). Actual epileptiform convulsions have been mentioned only by McLeod (1883) and Young and Hunter (1947).

The patient described here was first seen by one of us because she had had a number of generalized fits occurring during the course of a prolonged and unexplained febrile illness.

Case Report

A married woman, aged 52 years, was first seen on March 4, 1948, having had four or five epileptic attacks. At the age of six years she had an attack of rheumatic fever, and for a few years she suffered from intermittent joint pains. There was nothing to suggest that there was involvement of the heart at the time. She subsequently married and had two uneventful pregnancies. In 1937 glycosuria was found and she was treated as a diabetic by diet only. In the same year bilateral lens extractions were performed for cataract.

The present illness started in November, 1946, with attacks of fever and rigors, each attack lasting a few days followed by complete recovery. During these attacks there was some shortness of breath and palpitation, and in some there had been a complaint of left mammary pain radiating down the left arm, unrelated to exertion. She was admitted to St. Luke's Hospital, Guildford, in January, 1947. She had intermittent fever to about 101° F. and a persistent tachycardia (110–130). There was no clinical evidence of a heart lesion. Blood culture was negative. There was a mild microcytic anæmia with a polymorphonuclear leucocytosis varying between 17,000 and 40,000 per c.mm. The radiological appearance of the heart was said to suggest mitral stenosis. The lungs were normal. The Wassermann reaction was negative. There was then no evidence of diabetes. She was discharged at the end of five weeks at the request of her relatives.

She was admitted to the Royal Masonic Hospital in July, 1947, under the care of Sir Horace Evans, having had an attack of pleurisy with blood-stained sputum the previous month. On examination then, she appeared thin and sallow. There was no cardiac enlargement but a short presystolic bruit was heard. The spleen was palpable. There was a secondary anæmia with a white cell count that varied between 3000 and 12,000 per c.mm. Blood cultures were negative. The blood Wassermann and Kahn tests were positive. X-rays of the chest showed evidence of infarction of both lungs. A diagnosis of mitral stenosis with bacterial endocarditis was made and she was given penicillin two million units daily for a long period without material change in her condition. After returning home her condition remained much the same and she continued to have intermittent fever.

In February, 1948, she had a generalized epileptic attack without warning, which was not followed by any focal symptoms or signs. Further similar attacks occurred in the same month. She was seen by one of use for the first time in March, 1948, and appeared moderately wasted with a generalized *café-au-lait* tint to the skin. In addition there was some brownish pigmentation of

the forearms, abdomen, and hard palate. The pulse rate was 90 a minute, temperature normal and blood pressure 86/60. No cardiac abnormality was observed and the spleen was not palpable. Blood count was normal apart from a mild microcytic anæmia and blood culture was negative. The urine contained a moderate amount of pus with a growth of *B. coli* on culture. In view of the hypotension, pigmentation, and past history suggestive of endocarditis, it was considered possible that the suprarenal glands had been damaged by emboli with consequent Addison's disease. The administration of D.O.C.A. ten milligrams daily raised the blood pressure to a maximum of 116/85, but resulted in widespread œdema and was discontinued. In April, 1948, a systolic murmur was heard over the whole præcordium with a mid-diastolic murmur to the left of the sternum. Fluoroscopy showed slight backward displacement of the barium in the right oblique view; the right auricle was prominent in the anterior view. Three days later the diastolic murmur was no longer audible and a rough systolic thrill was felt. The presence of dyspnœa with an enlarged tender liver was taken to indicate cardiac failure but there was no engorgement of the neck veins or œdema. At this time the urinary infection became severe but responded to sulphonamide therapy in about three weeks, and the patient was discharged in June feeling fairly well but having occasional fever up to 101° F.

FIG. 1.

FIG. 2.

FIG. 1. and 2.—Gangrene of nose and symmetrical gangrene of feet.

She was re-admitted in July, 1948, complaining of increasing weakness and occasional shivering attacks. The physical signs were unchanged and there was an intermittent pyrexia to 102° F. The urine was normal. In spite of further negative blood cultures, it was considered that active endocarditis was present and a course of penicillin therapy was commenced, 125,000 units three-hourly. This was continued for thirty-eight days, the patient being afebrile for the last eighteen days. She was discharged on September 4 and re-admitted on November 11. She had been fairly well until four weeks before admission when she complained of frontal and occipital headache, with intermittent severe abdominal pain of sudden onset, associated with precipitate defæcation. These symptoms occurred about four times daily. Examination showed an extreme degree of emaciation with generalized brownish pigmentation of the skin and a malar flush. There was no cyanosis. The apical first sound had a snapping quality; there was a loud diffuse systolic murmur and a soft diastolic murmur to the left of the sternum, the latter audible in the erect posture only.

Two days later she was found to have a deep purplish discoloration of the tip of the nose, fingers, and feet with some purpuric patches at the elbows. Her temperature was 95° F. and her pulse rate 80 a minute, the pulse being almost imperceptible at the wrist. The diastolic murmur was audible in any posture. A diagnosis of ball thrombus in the left auricle was suggested at this stage by the variable physical signs, the clinical diagnosis of mitral disease, and the symmetrical peripheral gangrene.

During the next few days there were frequent attacks of auricular flutter with two to one block, each attack lasting a few minutes and not giving rise to any new subjective disturbance. The patient's condition became slowly worse without the development of any signs of congestive heart failure, and she died seven days after the onset of gangrene.

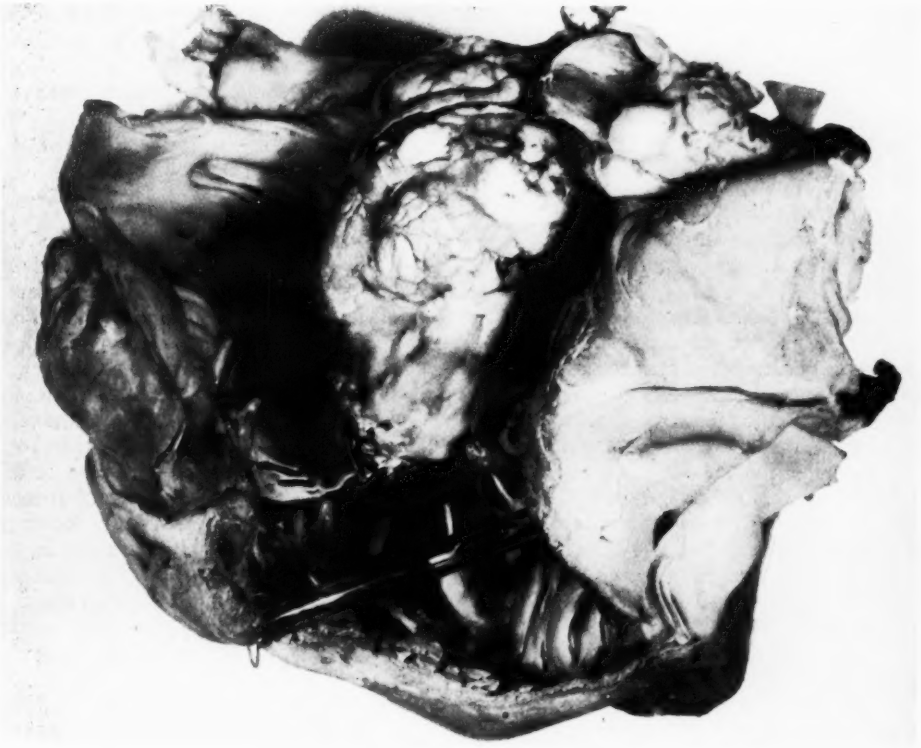

FIG. 3.—Cardiac myxoma exposed *in situ* showing origin from the inter-auricular septum, and the free end of the tumour lying in the tricuspid orifice.

Necropsy. There was evidence of infarction of the bases of both lungs. The pericardium was normal. The right auricle was considerably enlarged and the left ventricle unusually small. A large solid mass could be felt through the right auricular wall, and on opening this chamber a firm greyish-yellow mass was found arising from the inter-auricular septum in the region of the fossa ovalis and extending down into the tricuspid orifice. The latter was dilated, the surfaces of the valves were roughened and the points of contact of the mass with the valves could be clearly seen. The mitral, pulmonary, and aortic valves were normal and there was no evidence of recent or old endo-

carditis. The liver was enlarged and smooth and showed marked " nutmeg " change. The spleen was enlarged but appeared of normal texture.

Macroscopically, the intracardiac mass appeared on section to consist of a firm grey mucinous and semi-gelatinous substance with a slightly laminated organized thrombus covering the surface with some small discrete hæmorrhages.

Microscopically the tumour consisted of areas of spindle cells interspersed with a few stellate cells in a mucinous matrix, with externally, a firmly attached organized and partly necrotic thrombus. The myxomatous part of the tumour and the thrombus merged into one another with no dividing line. The vessels were very thin with single endothelial lining and there was considerable round cell and polymorphonuclear perivascular infiltration with phagocytic ingestion of hæmosiderin.

Several blocks were made, sections from one of which stained with the specific muci-carmine stained well, the others having much less affinity for this dye on account of the intense necrosis present. For the same reason Weigert's elastic stain demonstrated only a few fibres, usually abundant in the endocardial myxomata.

The tumour had, therefore, the histology and staining reactions of a myxoma associated with an intimately fused necrotic thrombus.

Discussion

This patient had an illness of five years duration, characterized by progressive wasting, and during the last two years by an intermittent pyrexia, hæmoptysis, palpitation, convulsions, and finally peripheral gangrene. In addition, there was a past history of rheumatic fever and glycosuria. For a time the diagnosis of mitral stenosis with an added endocarditis seemed quite clear, but the course of the illness and the persistently negative blood cultures ultimately made this diagnosis doubtful. Finally, the occurrence of symmetrical peripheral gangrene led to the suggestion that the supposed mitral stenosis was complicated by the presence of a ball thrombus in the left auricle. This seemed at the time to account for many of the unusual features of the illness, in particular the fits, the variable cardiac murmurs, and the intermittent enlargement of the liver and spleen.

The finding of a tumour in the right auricle without any evidence of mitral disease or of old endocarditis increased the difficulty of explaining certain of the symptoms and signs. It must be concluded that the fits were due to cerebral anoxia following temporary impaction of the tumour in the tricuspid orifice. (In theory they might have been associated with paroxysmal auricular flutter but there was no change in the pulse rate to suggest this during the two fits that were observed in hospital). The attacks of dyspnœa and the final gangrene could be explained in a similar way. The hæmoptyses could be explained by the occurrence of pulmonary infarction by detached fragments of tumour or its covering thrombus. The fever, leucocytosis, and the response to penicillin remained to be explained. The presence of a necrotic thrombus covering the tumour suggests that there had been in fact an endocarditis confined to the surface of the tumour, and that this infection had finally been controlled by chemotherapy.

There has been considerable doubt in the past as to the existence of cardiac tumours. Some have regarded them as organized thrombi. It is, however, now generally accepted that these masses have a neoplastic origin. (Welch, 1899; Ribbert, 1924; Yater, 1931; Fawcett and Ward, 1939).

The diagnosis of this condition during life is clearly very difficult, both on account of its rarity and of the great variability in the clinical manifestations. It is to be expected that symptoms directly attributable to the presence of an intra-cardiac mass would be very similar whether the mass is a myxoma or a ball (mass) thrombus. Evans and Benson (1948) reviewed the symptomatology of these two conditions, and pointed out the difficulty of dissociating the symptoms of the thrombus itself from those of the mitral stenosis that accompanies the condition. Variability of the clinical picture would seem to be the feature of real value, and the occurrence of intermittent congestive heart failure with perhaps syncopal attacks and peripheral cyanosis or gangrene should suggest

intermittent obstruction of the mitral or tricuspid orifices. Yater (1931) stated that every patient diagnosed as having tricuspid stenosis should be suspected of having a cardiac tumour, giving as his reason that " inflammatory stenosis of that orifice is exceedingly rare." This should perhaps be qualified by adding that evidence of mitral disease must be absent.

It was remarkable that the presence of a tumour or thrombus which almost completely obstructed the passage of blood through the heart was compatible with the continuation of life over quite a long period. Strouse (1938) described a patient who died in 1935 from myxoma of the right auricle the symptoms of which had been present for 43 years. The patient described by Macoun (1949) lived for four years and the patient here described lived for five years. In the latter it must be concluded that the obstruction of the tricuspid orifice was intermittent in the cardiac cycle. Since the main filling of the ventricle occurs during diastole it is probable that the tumour only obstructed the orifice during auricular systole.

The diagnosis of this condition during life is of great interest but the value of such a diagnosis is likely to remain essentially academic, since it is unlikely that any steps could be taken to remove an intra-auricular tumour; the comment of Burns (1809) is still mainly true: " if blended with other diseases its presence can rarely before death be ascertained; and if discovered it would not alter the plan of treatment."

SUMMARY

The clinical course is described of a patient who ultimately died of a myxoma of the right auricle. Among the features were: epileptiform convulsions, hæmoptysis, hypotension, and peripheral gangrene. The diagnosis was complicated by the presence of fever due to an endocarditis on the surface of the tumour.

We wish to thank Dr. William Evans for his advice, Dr. R. C. Matson for examining and reporting upon the pathological material, Dr. Aubrey Leatham for assistance with fluoroscopy, and Sir Horace Evans for the records of this patient during the early part of her illness.

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CORONARY EMBOLISM AND CORONARY OCCLUSION IN BACTERIAL ENDOCARDITIS

BY

BETTY WALKER

From the Metropolitan Hospital, London

Embolic occlusion of the peripheral vessels is common in bacterial endocarditis, especially during the terminal stages, but occlusion of the coronary artery in this disease is unusual at any time.

Virchow (1856) described coronary embolism in a case of recent endocarditis. Saphir (1933) surveying earlier reports of coronary embolism from all causes, found 35 cases reported since Virchow's original paper. Of these, only 15 came to necropsy. Appelbaum and Nicholson (1934) in an analysis of the pathological anatomy of 168 cases of occlusion of the coronary arteries cited four instances of coronary embolism in bacterial endocarditis, in three of which there was recent myocardial infarction as the result. In a survey of 2877 necropsies, Levy *et al.* (1934) found six examples of coronary embolism, but without mentioning the source. Among 12,300 consecutive necropsies, Garvin and Work (1939) reported three cases in which bacterial endocarditis was present and in two of them myocardial infarction had taken place, although in one the coronary arteries were affected by atheroma. Lutembacher (1939) and Caplan and Alpern (1943) each described a case of coronary embolism from bacterial endocarditis producing myocardial infarction. De Navasquez (1939) examined the heart histologically in 20 unselected cases of bacterial endocarditis and found emboli resembling fragments of vegetations in 80 per cent of them. In only one was there a visible infarct. He considered that the scarcity of myocardial infarcts was due to the small size of the occluded vessels, which in his series varied from 50 μ to 1·0 mm. in diameter.

The case of bacterial endocarditis described here is of interest, not only because coronary embolism is itself uncommon but because it presents the picture of a dual mishap to the coronary circulation, namely cardiac infarction from coronary embolism and later massive ischæmia from sudden occlusion of a coronary orifice by a vegetation on the aortic cusp. Lamb (1913) described a case of occlusion of a coronary artery by a pedunculated vegetation of the aortic valve.

Case Report

A woman, aged 43 years, was admitted to hospital with loss of weight, lassitude, anorexia, and dyspnœa on exertion over a period of six months. On one or two occasions, her sputum had been streaked with blood, but until then there had been no ill health and she had never had rheumatic fever. She was pale and anæmic (hæmoglobin 40 per cent). There was fever, clubbing of the fingers, and splenomegaly, and red blood cells were found in the urine. No petechiæ or tender nodes could be found and the blood culture was repeatedly negative. Increased arterial pulsation showed in the neck; the pulse was collapsing and the blood pressure was 135/55. The apex beat was displaced outwards towards the anterior axillary line. A diastolic thrill was felt in the mitral area where presystolic and mid-diastolic murmurs of mitral stenosis were heard. An early diastolic murmur of aortic incompetence was loudest at the lower part of the left border of the sternum. There were no signs of heart failure. The electrocardiogram was normal except for bifid P waves, and at cardioscopy there was moderate enlargement of the heart from aortic incompetence and mitral stenosis. The bacterial endocarditis was treated with two million units of penicillin daily for twelve weeks.

She made satisfactory progress, but at the end of the sixth week, she experienced severe pain, constricting in character, behind the breast bone, spreading into the left shoulder and down the left arm. The blood pressure fell to 105/50, but she gained relief from trinitrin in about ten minutes. An electrocardiogram (Fig. 1) taken four hours later showed a flat T wave in leads I and CR7 and an inverted T wave in CR4.

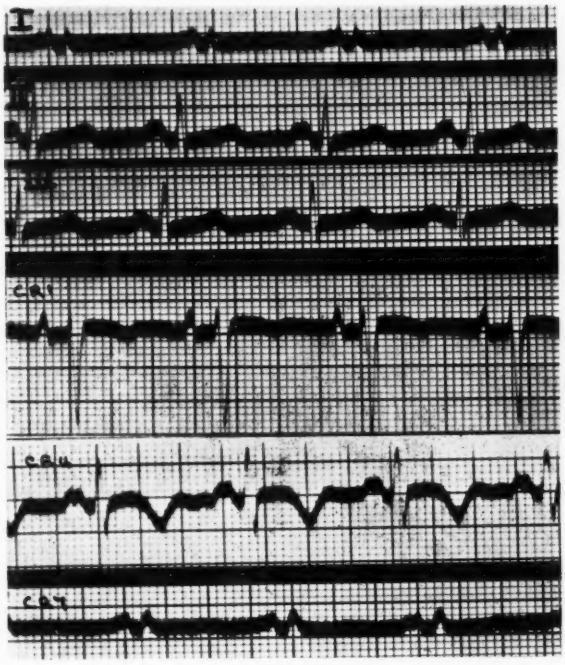

FIG. 1—Electrocardiogram taken four hours after the attack of cardiac pain. The T wave is flat in leads I and CR7 and is inverted in CR1 and CR4.

In view of the clinical episode and the subsequent cardiographic changes, the possibility of a coronary embolism was entertained. She had no further attacks of pain and the cardiogram remained unaltered, but seven weeks later, she sat up in bed and vomited and died unexpectedly.

Post-mortem findings. At necropsy there was an area of old fibrinous pericarditis approximately 2·5 by 1·5 cm. on the anterior wall of the left ventricle, near the lower end of the interventricular septum. The underlying myocardium was thinned and fibrotic and there was visible infarction. The coronary arteries appeared healthy and were patent; their main branches showed no macroscopic evidence of atherosclerosis, blood clot, or embolism. The aorta was healthy. The mitral valve admitted the tip of the little finger with difficulty; it was rubbery in consistency and a few friable vegetations were present. The left atrium was moderately dilated. All three cusps of the aortic valve were thickened and almost completely destroyed and replaced by large friable vegetations, one of which measuring 1·5 by 0·75 cm. occluded the mouth of the right coronary artery (Fig. 2). The spleen was enlarged and septic and it showed infarcts, as did the kidneys.

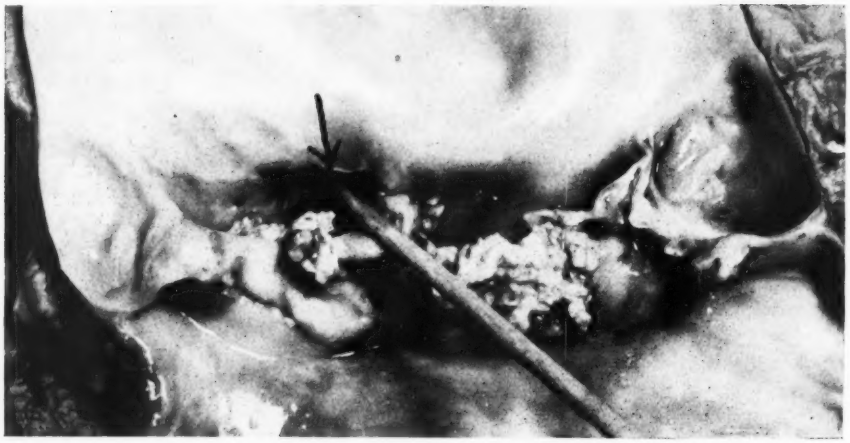

FIG. 2.—Photograph of aortic cusps and coronary ostia showing probe (marked by arrow) in right coronary artery after vegetation had been removed.

Conclusion

A patient is described in whom bacterial endocarditis affecting the aortic valve produced cardiac infarction from a coronary embolism. There was recovery from this, but sudden death took place seven weeks later from complete occlusion of the orifice of the right coronary artery by a vegetation which had spread from the adjoining aortic cusp.

I wish to express my thanks to Dr. N. G. Hulbert for his kind permission and encouragement to publish this case, and to Dr. William Evans for his valued criticism and advice.

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CONGENITAL AORTIC ANEURYSM WITH VALVULAR STENOSIS AND DISSECTING ANEURYSM

BY

C. P. PETCH

Medial necrosis of the aorta is often associated with dissecting aneurysms that occur early in life. In the case described this defect was combined with a true aneurysm and aortic valvular stenosis.

Case Report

A man of 35 was admitted to hospital with a presumptive diagnosis of coronary thrombosis. He had been found to have a cardiac murmur at the age of five, but his activities had never been restricted. There was no history of rheumatism of or syphilis. The abnormality of his heart had been noticed again during his service in the Army, and had resulted in his being downgraded from category A1 to C3. After returning to civil life he had continued work in an office without illness until the day before his admission to hospital. On that day his first symptom had been a sense of tightness in the chest, which gradually developed into a severe substernal pain spreading to both shoulders. It was continuous, worse on breathing and on movement, and made him sweat profusely. He did not vomit or feel short of breath.

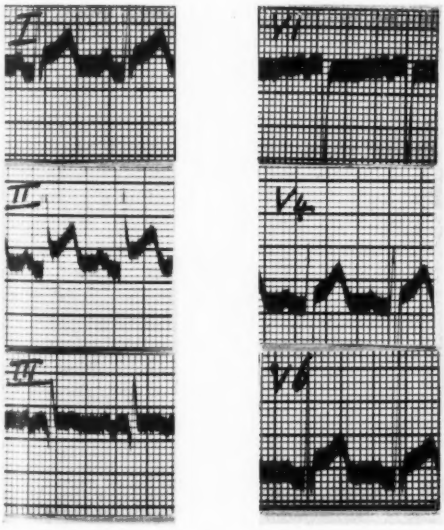

FIG. 1.—Electrocardiogram showing elevation of S–T segments in leads I, II, V4 and V6.

On admission his temperature was 101° F.; pulse regular at 110; blood pressure 100/80. His heart was observed to be enlarged to the left and a pericardial friction rub was heard. There were no signs of cardiac failure and the other systems were normal. Arachnodactyly was not found. The next morning the pericardial friction had gone, and a harsh basal systolic murmur with a soft blowing diastolic was audible. At the apex there was a systolic murmur but no diastolic. An electrocardiogram (Fig. 1) was chiefly remarkable for the elevation of the S–T segment in leads I, II, V4 and V6, with preservation of the R wave in the præcordial leads; it was regarded as being compatible with acute pericarditis. White blood cells at this time numbered 9200, 76 per cent being polymorphs. During the next five days the pain decreased and the fever subsided gradually to normal. On the fifth day he died without warning.

Necropsy report. A large hæmopericardium was found. The ascending aorta was the site of a thin-walled aneurysm about the size of a grapefruit which had ruptured by a horizontal split

7 cm. long between 5 and 7 cm. above the valve (Fig. 2). Dissection between the coats of the aorta had occurred downwards to the pericardium but not to any extent upwards, and the true aneurysm rather than the dissection was the striking feature. The intima was quite smooth. The aortic valve was stenosed, admitting only one finger. The two posterior cusps were fused, and the whole

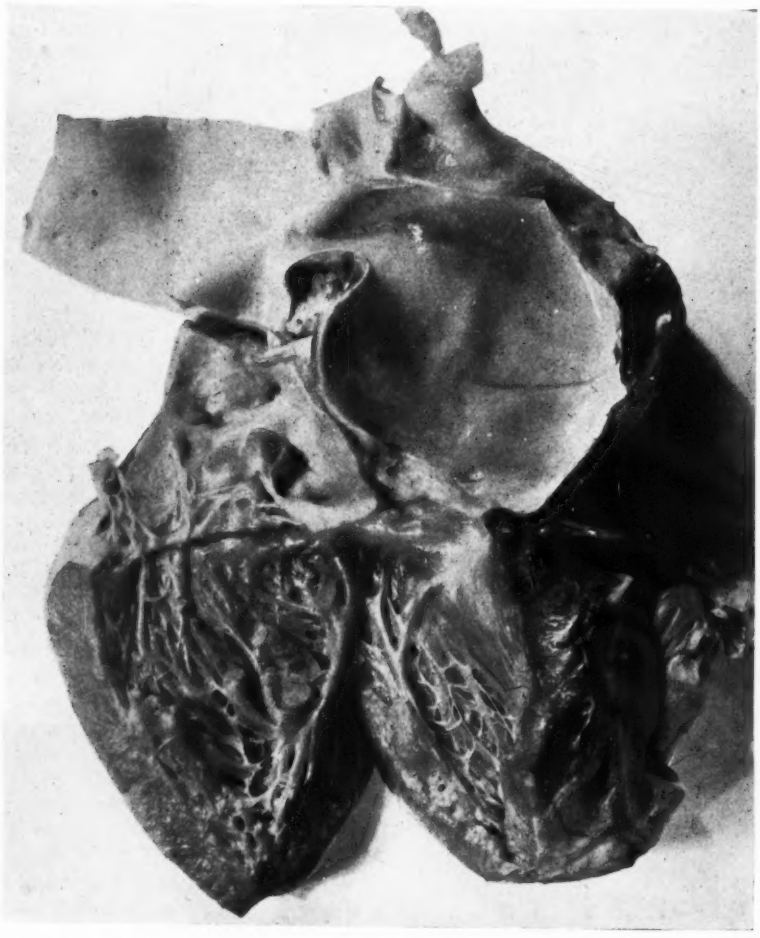

FIG. 2.—The left ventricle and ascending aorta opened; the split appears as a horizontal line in the intima. (× 3/5 natural size.)

structure was calcified and incompetent. There was a slight narrowing of the lumen of the aorta in the region of the ductus, which was closed, but true coarctation was absent. No other significant abnormality was found, the coronary arteries being patent, the myocardium healthy, and the cardiac septa intact. On microscopy, sections of the aorta showed mucoid degenerative changes and fragmentation of elastic fibres in the media.

Comment

Schnikter and Bayer (1944) collected 141 cases of ruptured dissecting aneurysm of the aorta under the age of 40, and drew attention to the frequent association of other defects. Cystic medial necrosis was held to be the underlying abnormality. A congenital narrowing of the aorta in the region of the isthmus was found in 32 per cent, but aortic valvular stenosis was described only once. These authors also referred to the liability of these subjects to rheumatic heart disease, though in the present case the early recognition of the murmur may indicate a congenital valvular lesion. Saccular aneurysm of the ascending aorta was not found in this series, but Baer *et al.* (1943) described two cases in which such an aneurysm was found in this site and was considered congenital. Again, the condition of the media was thought to be the cause. These aneurysms did not rupture or dissect but the patients died young, at the ages of 13 and 26. Both had arachnodactyly, cardiac hypertrophy, and other defects. Reynolds (1950) has also discussed the association of aortic aneurysms and dissecting aneurysms with arachnodactyly. The present case had the same typical changes in the media, but differed from both groups in its subsequent progress, in that a saccular aneurysm was formed that ruptured to cause death.

Summary

Rupture of a congenital saccular aneurysm of the aorta at the age of 35 is described. Medial necrosis was found; the aortic valve was stenosed.

I am indebted to Dr. T. Goodier for the post-mortem examination and to Dr. W. G. Millar for the photograph.

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ABSTRACTS OF CARDIOLOGY

Pulmonary Atresia and the Collateral Circulation to the Lungs. K. D. ALLANBY, W. D. BRINTON, M. CAMPBELL, and F. GARDNER. *Guy's Hosp. Rep.*, **99**, 110–152, 1950. 22 figs., 22 refs.

The clinical and anatomical features in 6 cases of pulmonary atresia are described. In one patient, aged 15, with a closed ventricular septum, the pulmonary circulation was maintained by a widely patent ductus communicating with a grossly dilated pulmonary artery; the conclusion was reached that the pulmonary blood supply in this instance was better than in many cases of tetralogy. The other 5 cases were of pulmonary atresia with high ventricular septal defect and over-riding aorta. Atresia was usually at, or near, the pulmonary valve, the pulmonary artery being small, but patent distal to the atresia. Abnormally large bronchial arteries were found in every case and in some were joined directly with branches of the pulmonary artery. The development and classification of these vessels is discussed. The authors feel that this group of cases with pulmonary atresia should be separated from their conventional classification with the tetralogy and be considered as a distinct entity; only cases with pulmonary stenosis should be defined as the tetralogy of Fallot. On the clinical side the authors make the point that in pulmonary atresia a systolic murmur is generally absent and the second sound in the pulmonary area, is louder than in the tetralogy. [The article is exceptionally well illustrated and repays close study.] *James W. Brown*

Pheochromocytoma and Essential Hypertensive Vascular Disease. M. GOLDENBERG, H. ARANOW, A. A. SMITH, and M. FABER. *Arch. intern. Med.*, **86**, 823–836, Dec., 1950.

This is a comprehensive paper based on the findings in 22 cases of pheochromocytoma, of which the clinical histories are given. These tumours contain adrenaline and noradrenaline in varying proportions. Continuous intravenous infusion of the former raises the systolic blood pressure, causes hyperglycæmia, augments the basal metabolic rate (B.M.R.), and produces anxiety and palpitations, whereas noradrenaline raises both the systolic and diastolic pressures, has little effect on the B.M.R., and produces the picture of classical essential hypertension, which may be mimicked in cases of pheochromocytoma.

It was found that in 7 of the 12 cases in which the pheochromocytoma was removed surgically the hypertension continued after the operation but, strangely enough, the symptoms disappeared. It would appear that although the primary stimulus had ceased, the hypertension was irreversible [compare the results of nephrectomy for hypertension]. Chemical analysis of 15 of the tumours was undertaken and it was found that where the tumour contained a large amount of adrenaline, the clinical picture was one of tachycardia, high B.M.R., and hyperglycæmia, whereas small tumours, which contained only noradrenaline, produced the pure picture of essential hypertension. The former group usually showed a strong positive reaction to the piperoxan hydrochloride test. *Paul B. Woolley*

The Ventricular Electrokymogram. L. C. AKMAN, A. J. MILLER, E. N. SIBLER, J. A. SCHACK, and L. N. KATZ. *Circulation*, **2**, 890–899, 1950. 8 figs., 17 refs.

The apparatus used in this study consisted of a Sanborn electrokymograph and a Sanborn stethocardiette for recording of the heart sounds, which were used for time reference. Over 200 left ventricular electrokymographic tracings were obtained in 32 young healthy adults. On the average six different sites over the left ventricle were explored in each case; the curves obtained were analysed and compared. The authors present in two tables the relevant measurements and the range of variation as between one tracing and another in the same individual. The contour variations are described in detail and illustrative examples reproduced.

It is concluded that variations in contour and time sequence of events in the normal electrokymogram are considerable. These variations are caused not so much by changes in cardiac volume as by positional movements of either the whole or parts of the heart. Furthermore, it was found that there was no consistent moment-to-moment time relationship between electrokymograms obtained at various sites on the left ventricular border and the heart sounds.

It is pointed out that certain curve patterns hitherto described as abnormal and characteristic of myocardial infarction and constrictive pericarditis might occur as a normal variant in electrokymograms from healthy hearts. *A. I. Suchett-Kaye*

Intravenous Use of Quinidine, with Particular Reference to Ventricular Tachycardia. A. H. CLAGETT. *Amer. J. med. Sci.*, **220**, 381–388, 1950.

Although quinidine has been given by mouth in the treatment of ventricular tachycardia since 1922 there are comparatively few references in the literature to its intravenous use. Out of 97 recorded cases, of which 62 were of paroxysmal ventricular tachycardia, in 42 the rhythm reverted to normal and only in 11 cases did reactions occur, 4 of which (all in the same series) were fatal.

In the authors opinion, the intravenous injection of

quinidine is justified when rapid action is needed or when the patient is unable to take it by mouth owing to gastro-intestinal upset. He uses ampoules of quinidine lactate containing 0·65 g. in 10 ml. and adds one of these to 50 ml. of 5% glucose, giving the solution intravenously at approximately 2 ml. a minute.

The treatment of 13 cases is described in detail.

M. H. Pappworth

Text Book of Radiological Differential Diagnosis. Vol. I. Diseases of the Thoracic Organs. (Lehrbuch der Roentgenologischen Differential Diagnostik Band. I Erkrankungen der Brustogane). WERNER TESCHENDORF, Cologne. Gearg Thieme: Stuttgart, 1950.

This volume gives a carefully thought out description of the radiology of the chest including the œsophagus. The first half of the book deals with diseases of the lung and pleura.

The author gives an interesting account of the differential diagnosis of aortic aneurysm, pointing out that whereas the kymograph accurately records the movements present, these may be absent in the aneurysmal sac owing to clot, but present in some cysts owing to transmitted pulsations.

The section on the heart, which comprises about one-fifth of the book, deals first with methods of measurement of heart size using orthodiagrams and teleradiography. The uses of kymography are thoroughly discussed, one of the advantages of which is that the amplitude and form of the waves can be used as a method of assessment of heat function.

There is a short section on congenital abnormalities of the heart, but angiocardiography is not discussed except to point out its potential dangers. The changes seen in disturbances of heart rhythm in the kymograph are contrasted with their much more exact demonstration by electrocardiography. Some interesting illustrations of kymographs are given of patients with heart block, especially complete heart block when the slow rounded ventricular waves with lateral plateau formation are well seen. In some cases the more rapid auricular contractions are discernible.

Diseases and abnormalities oft he œsophagus are discussed, and the last part of the book deals with the diaphragm.

This book is beautifully produced with clear print and marginal summaries of each paragraph. The 865 illustrations are all very good and show the points under discussion clearly. It is a compendium of information and is strongly recommended as a reference book and also as a textbook for students of chest radiology. There is an excellent bibliography.

F. G. Wood

Left Ventricular Pressures in Patients with Aortic Insufficiency Studied by Intracardiac Catheterization. H. A. ZIMMERMAN. *J. clin. Invest.*, **29**, 1601–1603, Dec., 1950.

The pressure levels within the left ventricular cavity have been studied in 10 human subjects with aortic insufficiency by catheterization of the left ventricle via the radial artery. The 3 patients who exhibited no clinical evidence of congestive failure had normal left ventricular diastolic pressures. The 7 patients in obvious congestive failure demonstrated significant increases in diastolic pressure averaging 25 mm. of mercury.—[Author's summary.]

Pulmonary Hypertension in Mitral Stenosis. R. I. S. BAYLISS, M. J. ETHERIDGE, and A. L. HYMAN. *Lancet*, **2**, 889–894, Dec. 30, 1950.

In 22 patients with mitral stenosis the right ventricular and/or pulmonary artery pressures have been correlated with clinical, radiological, and electrocardiographic findings. Pulmonary hypertension at rest was found in 17 patients. In general, those with the most severe symptoms had the highest pressures, but the duration of symptoms was not related to the degree of pulmonary hypertension.

Patients with severe pulmonary hypertension without peripheral venous congestion presented a recognizable syndrome, characterized by predominant pulmonary symptoms and electrocardiographic evidence of right ventricular hypertrophy. Patients with lesser degrees of pulmonary hypertension did not present characteristic features, but right ventricular enlargement on fluoroscopy was a constant finding. The degree of pulmonary hypertension, however, can be determined only by direct measurement. Right ventricular enlargement was found in all patients with pulmonary hypertension. There was no relation between the size of the left atrium and the degree of pulmonary hypertension.

On exercise a striking rise in pulmonary artery pressure occurred without a significant increase in cardiac output. The pulmonary hypertension at rest and on exercise is due to stenosis of the mitral valve and to increased pulmonary arteriolar resistance. The relative importance of these two factors is discussed.—[Authors' summary.]

Effects of Exercise on Circulatory Dynamics in Mitral Stenosis. III. R. GORLIN, C. G. SAWYER, F. W. HAYNES, W. T. GOODALE, and L. DEXTER. *Amer. Heart J.*, **41**, 192–203, Feb., 1951.

The authors report 9 observations on 8 cases of mitral stenosis with minimal disease of other valves. All but the most severe clinical grades of stenosis were represented, only patients thought to be unable to exercise safely being excluded. Despite this selection, 3 patients developed pulmonary œdema during the investigation.

Pulmonary "capillary" pressure was recorded at rest, and then during exercise performed (while recumbent) on a bicycle ergometer. Exercise increased the oxygen consumption to 1·5 to 3 times the resting level. In 8 observations there was no change in arterial oxygen saturation, and in the 5 patients with a low fixed cardiac output there was a proportional increase in arteriovenous oxygen difference. The mean resting pulmonary "capillary" pressure was raised in all cases and further increased with exercise. The pulmonary arterial pressure rose with the pulmonary "capillary" pressure, and the "PA–PC" gradient was unchanged, or rose only 1 to 15 mm. Hg. The calculated pulmonary arteriolar

resistance was unchanged by exercise in 2 cases, and rose in 2 cases.

The authors suggest that cardiac output becomes fixed in mitral stenosis because of: (1) the very high pulmonary arteriolar resistance, (2) the limitation of the patient's effort by pulmonary congestion, and (3) the decrease in stroke volume of the right ventricle resulting from the fixed output and the tachycardia on exercise. Three patients were othopnœic at rest and had high resting pulmonary "capillary" pressures (26 to 34 mm. Hg). On exercise these patients developed pulmonary œdema, with a rise in pulmonary capillary pressure to 35 to 47 mm. Hg. In other cases, in which the resting value was lower, no œdema developed despite a rise above 35 mm. Hg on exercise. *D. Verel*

Mural Thrombosis and Arterial Embolism in Mitral Stenosis. A Clinico-pathologic Study of Fifty-one Cases. R. A. JORDAN, C. H. SCHEIFLEY, and J. E. EDWARDS. *Circulation*, **3**, 363–367, March, 1951.

Out of 11,536 necropsies performed at the Mayo Clinic during the 20-year period 1929 to 1948 there were 51 cases of mitral stenosis with intracardiac mural thrombi. Of the 42 cases in which mural thrombi were present in the left side of the heart (including 15 in which the right side was also involved) they were restricted to the auricular appendage in only 20. It would seem, therefore, that surgical resection of the left auricular appendix in such patients would offer no more than a 50% chance of eliminating the source of systemic arterial emboli. On the other hand, right atrial thrombi were restricted to the auricular appendix in 20 out of 24 cases, but embolism from thrombi in peripheral veins would still have to be reckoned with when considering surgical resection or obliteration of this appendix for repeated pulmonary infarction. *T. Semple*

The Natural History of the Electrocardiogram in Mitral Stenosis. [In English]. H. RASMUSSEN and J. BOE. *Cardiologia*, **18**, 33–44, 1951.

Serial electrocardiograms (standard limb leads) were recorded in 50 patients with mitral stenosis over periods ranging from 1 to 18 years (average 6 years). The findings confirmed the presence in such patients of "characteristic, but not specific, electrocardiographic changes." In 18 cases they observed the development in lead I of a low R, a broad-based straddling R, notching of R, or a second small wave following the main R wave. In 11 cases right axis deviation developed, while in 7 a right ventricular retardation (type I) developed. In attempting to correlate the presence of these changes with the size of the heart, it was noted that of 17 patients in whom there was considerable increase in size of the heart, 15 had electrocardiographic changes, while of 18 with no increase in size of the heart, 12 had such changes. For 10 years or more no changes might be noted, then within a matter of months marked changes would occur. This is taken to be an argument in favour of the view that dilatation rather than hypertrophy of the right ventricle is the main factor responsible for the electrocardiographic changes. Six unipolar præcordial leads were used in the final records taken on all 50 patients and showed relatively few significant changes compared with the limb leads. When first observed, 21 of the patients had sinus rhythm, compared with only 9 at the final examination. The corresponding figures for persistent auricular fibrillation were 24 and 39.

William A. R. Thomson

Surgery of Stenotic Valvular Disease of the Heart. R. P. GLOVER, C. P. BAILEY, and T. J. E. O'NEILL. *J. Amer. med. Ass.*, **144**, 1049–1057, Nov. 25, 1950.

In this review of the development of intracardiac operations for stenotic valvular disease, the results so far obtained in Philadelphia are described.

Congenital pulmonary stenosis. Eight cases have been operated upon with no death. In cases of the valvular type of stenosis (4 cases) the Brock technique was used, but for the infundibular type of stenosis (4 cases) a segment of septal tissue is removed with a sharp bone rongeur through an incision in the myocardium extending vertically above and below the septal ridge and at right angles to it. The early results at least equal those obtained by shunt procedures.

Mitral stenosis. In cases suitable for operation there should be no evidence of rheumatic activity, and sinus rhythm should be normal. Uncontrolled cardiac failure or appreciable left ventricular enlargement is a contraindication. Commissurotomy has been performed on 50 patients with 8 deaths. On the criteria of clinical disappearance of presenting symptoms and the reduction of left auricular and over-all heart size, excellent results have been obtained in 20 cases. The remainder have been improved.

Aortic stenosis. The contracted aortic valve can be approached from below via the left ventricle or from above via the common carotid artery. A Brock type of operation was performed on one patient, but the resulting aortic regurgitation caused the death of the patient. In two further cases the valve was successfully enlarged by passing a special dilator through the valve opening from above via a cervical incision into the right common carotid artery. *R. Lambert Hurt*

Atrial Flutter. II. Methods of Treatment. G. R. HERRMANN and M. R. HEJTMANCIK. *Amer. Heart J.*, **41**, 182–191, Feb., 1951.

The authors review published accounts of the treatment of auricular flutter and analyse the results in 93 episodes occurring in 82 new cases. In 28 cases in which the flutter was of less than 72 hours' duration sinus rhythm returned without therapy in 8. In flutter lasting more than 72 hours digitalis folia was effective in 19 of 24 cases, 7 being left with persistent fibrillation. Digitalis glycosides were effective in 5 of 8 cases, one persisting in fibrillation. Quinidine was effective in 11 of 21 cases, and with digitalis in 4 of 8 cases. Intravenous procaine failed in 2 cases.

The authors conclude that digitalis folia is the drug of choice in flutter where there is serious heart disease. Quinidine orally is effective, but should be given only in the absence of contraindications. In refractory cases intravenous quinidine may be tried, with constant observation of blood pressure and pulse rate. *D. Verel*